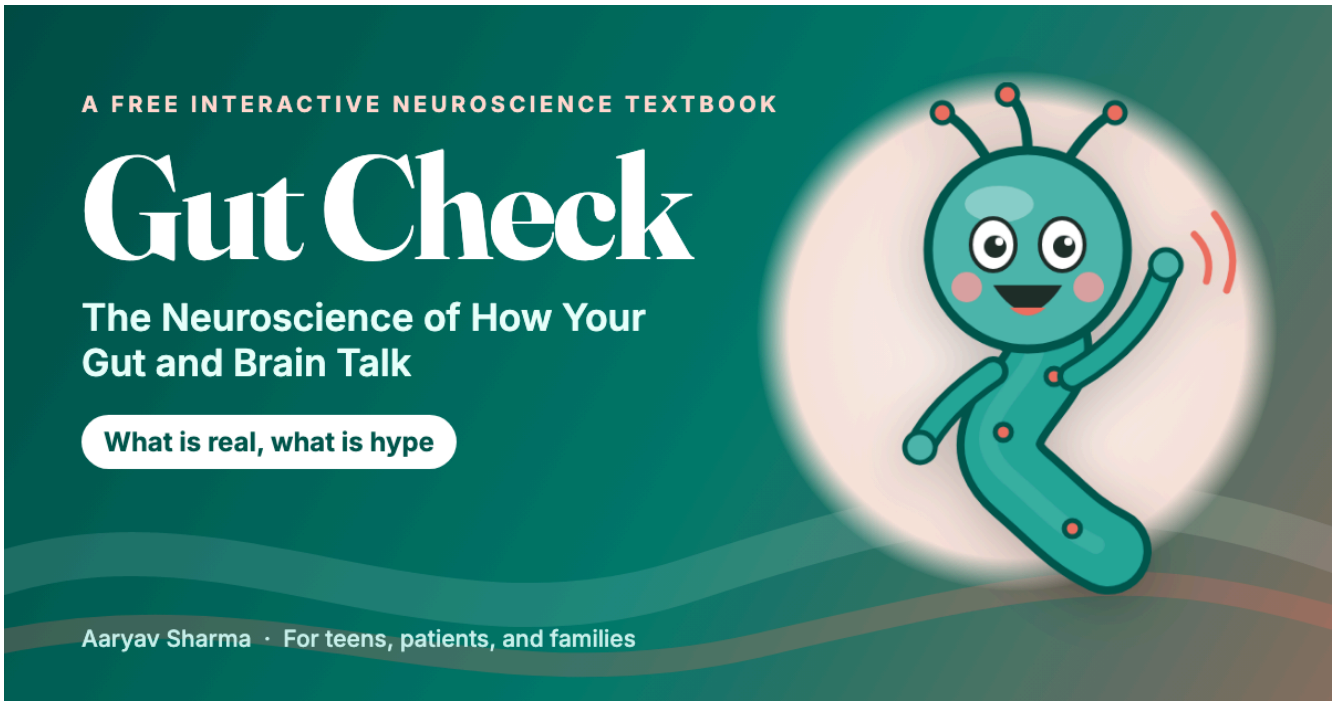
Gut Check: The Neuroscience of How Your Gut and Brain Talk



A free, interactive neuroscience textbook for teens, patients, and families. What is real, what is hype.

Your gut has its own network of hundreds of millions of neurons, trillions of microbes, and a large share of your body's antibody-making cells, and all of them send signals to your brain. That conversation helps explain why stress can upset your stomach, why gut diseases so often travel with anxiety and depression, and why so many "heal your gut, fix your mind" posts sound convincing. Among adults with inflammatory bowel disease, about one in three report anxiety symptoms and about one in four report depression symptoms.[1] In 2025, about one in three US high school students (33.3%) reported persistent feelings of sadness or hopelessness.[2] This book teaches the real neuroscience behind the gut-brain connection, and it grades every popular claim for how strong the evidence actually is.

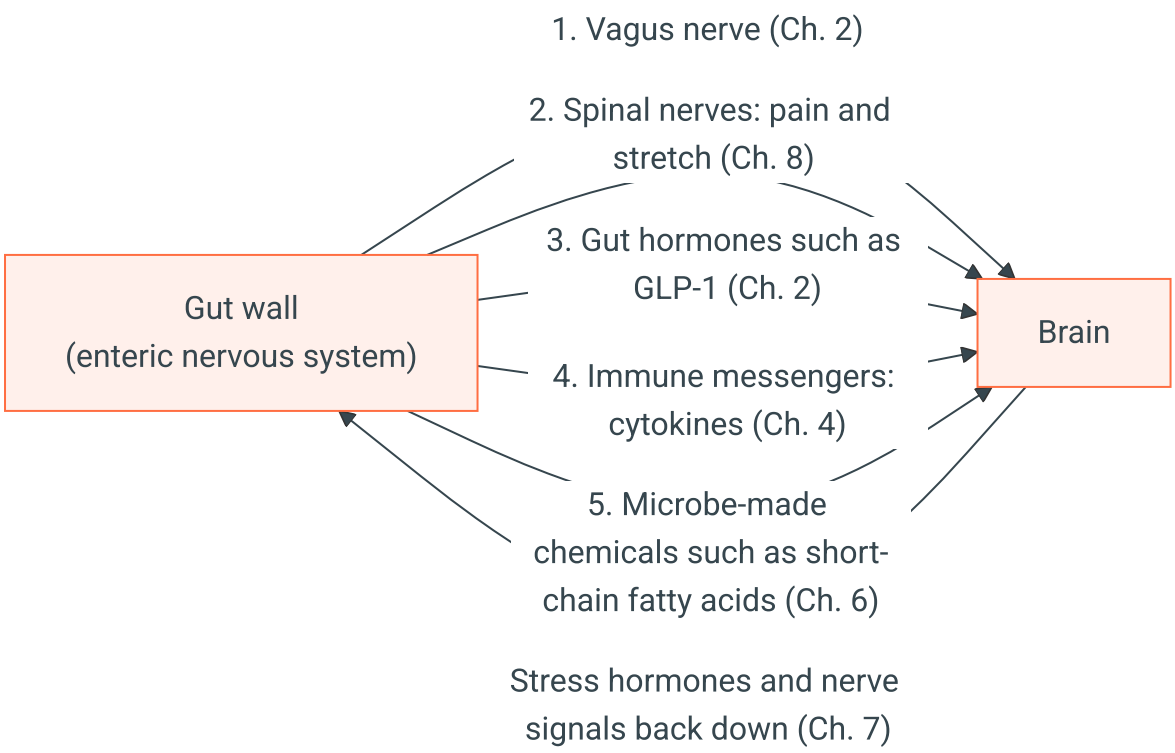
Hi, I'm Vee!



I'm a cartoon vagus nerve, the long nerve that carries messages between your gut and your brainstem. Most of my real-life fibers carry news *up* from the gut, so I hear a lot of gossip from down there. Let's check what the gut is really telling the brain!

Five ways your gut talks to your brain

The gut and brain stay in touch through several routes at once. Each one has its own chapter.



The arrows run both ways, which is why stress can upset your stomach and a flare can change your mood. The strength of the evidence differs a lot between routes; the Hype Meter shows which links are solid in people and which come mostly from mice.

What makes this book different

The Hype Meter

Every popular claim gets a visible grade: **Strong**, **Moderate**, **Preliminary**, or **Hype**. You'll always know whether a finding comes from mice or people, and whether it shows correlation or cause.

Hands-on simulations

Every chapter has an interactive MicroSim. Build a wave of peristalsis, turn up the stress dial, amplify a pain signal, or run a fake probiotic trial and watch chance fool you.

The patient and family side

Each chapter has an **At the Bedside** case that includes mood, stress, sleep, and school, plus

Free and open

No account, no ads, no paywall. Licensed CC BY-NC-SA 4.0, works on a phone, and anyone can suggest a fix on GitHub.

sidebars for families and for teens living with a gut condition.

Start here

- **New to the topic?** Begin with Chapter 1: The Brain in Your Belly.
- **Living with Crohn's, colitis, IBS, or celiac disease?** Start with Chapter 9, Chapter 10, or Chapter 12, and see Questions to Ask Your Doctor.
- **Here for the mental-health side?** Read Chapter 11: Anxiety, Depression, and the Gut.
- **Tired of wellness hype?** Learn how the Hype Meter works, search every graded claim in the Claim Explorer, then jump to Chapter 20: Be Your Own Scientist.
- **A parent, sibling, or friend?** See For Families.
- **Teaching or running a club?** See For Teachers, the Club Kit, and the PDF downloads.
- **Want to know how it was made and checked?** Read How This Book Was Made and Accuracy and Corrections.

What's inside

20 chapters in 5 parts	From the gut's own nervous system to reading health claims like a scientist
20 interactive MicroSims	Simulations you control, plus an interactive learning graph
Hype Meter grades	On the most common gut-brain claims, from "90% of serotonin" to "leaky gut"
A case in every chapter	Crohn's disease, IBS, celiac disease, Parkinson's disease, depression, and more
200 quiz questions	Ten per chapter, each with an explanation
A learning graph	337 concepts mapped so you learn prerequisites first
Appendices	A mock exam, a glossary, a teacher guide, a club kit, a pilot study kit, and a printable list of questions to ask your doctor

Part of a series

Gut Check is the second book by the same author. The first, *From Neuron to Bedside*, teaches how the brain works. This one teaches how the brain is wired to the rest of the body. You don't need to read the first book, but chapters link to it when a refresher helps.

Important

This book is for education only. It is **not medical advice**, and it cannot diagnose anything. The people in the cases, including Riya and Sam, are fictional. Never start, stop, or change a medicine, diet, or supplement because of something you read here; talk to your doctor. If you are in crisis, call or text **988** in the US.

Gut Check is an independent student project. It is **not affiliated with or endorsed by** any patient organization, hospital, university, or company.

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1. Barberio B, Zamani M, Black CJ, Savarino EV, Ford AC. (2021). Prevalence of symptoms of anxiety and depression in patients with inflammatory bowel disease: a systematic review and meta-analysis. *The Lancet Gastroenterology & Hepatology*, 6(5), 359-370. PubMed ↩
2. Kiplagat SJ, Verlenden JV, et al. (2026). Unmet need for mental health counseling or therapy among US high school students with persistent sadness or hopelessness: Youth Risk Behavior Survey, United States, 2025. *MMWR Supplements*, 75(1), 35-43. CDC ↩

About This Book

Why does this book exist?



Because a teen living with a gut condition, or anyone scrolling past "heal your gut" posts, deserves a clear, honest, free explanation of how the gut and brain actually talk.

The problem

The gut-brain connection is everywhere online, and much of it is oversold. Real research shows that the gut's own nervous system, the vagus nerve, gut microbes, and the immune system all send signals to the brain. But many claims built on that research go far beyond it, often to sell a supplement, a test kit, or a diet.

Teens with gut conditions rarely get the science explained. Inflammatory bowel disease, IBS, and celiac disease often travel with stress, pain, anxiety, and low mood. Patient guides are helpful but short, and research books are written for graduate students and cost money.

I could not find a free, textbook-length, high-school-level, interactive book on the neuroscience of the gut-brain axis. General textbooks teach digestion and the nervous system in separate chapters. Searching is not proof that nothing exists, so if you know of one, please tell me.

What this book does

- **Grades the evidence.** Every popular claim gets a Hype Meter grade, and every study is labeled as mouse or human, correlation or cause.
- **Explains the idea before the vocabulary.** Every new idea starts with an everyday comparison.
- **Lets you try things.** Every chapter has an interactive simulation, with a note on what the model leaves out.
- **Includes the patient and family side.** Every chapter has a fictional case that covers mood, stress, sleep, and school, plus sidebars for families and for teens living with a gut condition.
- **Gives you practice.** Every chapter has a Your Gut Check section, exercises at every level of Bloom's Taxonomy, and a quiz.
- **Stays free.** It's licensed CC BY-NC-SA 4.0 and hosted on GitHub Pages.

Who it's for

- High school students (grades 9 to 12) curious about the brain, the body, and medicine
- Teens living with Crohn's disease, ulcerative colitis, IBS, celiac disease, or stress-related gut symptoms
- Parents, siblings, and friends who want to understand (see For Families)
- Teachers running a biology, health, or neuroscience unit or club (see For Teachers)

The only prerequisite is one year of high school biology.

About the author

Aaryav Sharma (ORCID 0009-0006-3333-0809) is a high school student in Minnesota who plans to study neuroscience and medicine. He also wrote *From Neuron to Bedside*, a free interactive neuroscience textbook. A close family member lives with ulcerative colitis, which is a big part of why this book exists.

How this book was made, and how AI was used

I chose the topic, set the structure and the rules for every chapter, and decided how the book would grade evidence. I used Claude Code and Dan McCreary's open-source intelligent-textbook skills to help research, draft text, and build the simulations, and to run several separate rounds of fact-checking and editing.

Because AI helped write this book, mistakes are possible, and accuracy matters a lot in a book about health. The Accuracy and Corrections page explains how the book is checked and lists every fix. If you find an error, please tell me through the Contact page.

Acknowledgements

- **Dan McCreary** and the open-source intelligent-textbook skills, which made this workflow possible
- **MkDocs** and **Material for MkDocs** for the website framework
- **p5.js** for the simulations and **vis-network** for the learning graph viewer
- The **NIH**, **CDC**, **FDA**, the **Rome Foundation**, and **OpenStax** for freely available, trustworthy information

Disclaimers

- This book is for education only. It is **not medical advice** and cannot diagnose any condition. Talk to a doctor about symptoms, treatments, diets, or supplements.
- The people in the cases, including Riya, Sam, and Leo, are fictional composites.
- *Gut Check* is an independent student project. It is not affiliated with or endorsed by any patient organization, hospital, university, or company.

How to Use This Book

Two ways to read



Read straight through for the full story, or jump to the chapter you need. Every chapter lists its prerequisites at the top, so you'll know what to read first.

How a chapter works

Every chapter follows the same pattern, so you always know where to look.

Section	What it does
Summary, Concepts, Prerequisites	What you'll learn and what to read first
The hook	A real-world story, often about Riya (who has Crohn's disease) or Sam (who has IBS and test anxiety)
Core science	The neuroscience, starting with an everyday comparison before the technical words
Hype Meter cards	Grades on popular claims: Strong, Moderate, Preliminary, or Hype (how it works)
How to read a gut-brain claim	Six questions applied to one real study
For families / If you're going through this	Practical notes for loved ones and for teens with the condition
MicroSim	An interactive simulation, plus a box on what the model leaves out
At the Bedside	A fictional case from symptoms to mechanism, including the mind-body side
Common Misconceptions	Myths and their corrections

Section	What it does
Your Gut Check	Grade a claim, reason through three scenarios, and read real data
Exercises	12 questions across Bloom's Taxonomy, from Remember to Create
Key Takeaways and Quiz	A summary and a 10-question self-check with explanations

For students

1. Read the hook and the everyday comparison first. They make the hard parts easier.
2. Play with the MicroSim before and after reading the section it belongs to.
3. Try every Your Gut Check question before opening the answer.
4. Take the quiz. If you miss a question, the explanation names the concept it tested so you can go back and review it.
5. Use the glossary and the learning graph when a term is unfamiliar.

For teens living with a gut condition

Read at your own pace. The **If you're going through this** boxes are written for you. Bring questions to your care team; the printable Questions to Ask Your Doctor can help. This book explains the science; it can't tell you what's right for your body.

For families

Start with For Families, then read the chapter that matches your teen's condition.

For teachers and clubs

See For Teachers, the Teacher Guide, and the Club Kit. Every MicroSim page has a lesson plan and an embed code. The PDF downloads work for printing.

Accessibility

The book works on phones and tablets, supports dark mode (the toggle at the top of the page), and every simulation includes a text description for screen readers. If something doesn't work for you, please tell me.

Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading)

Summary

Your gut has its own nervous system, the enteric nervous system, built into the wall of the digestive tract. It contains hundreds of millions of neurons and can run digestive reflexes, such as the wave of squeezing that pushes food along, without any command from the brain. This chapter tours the gut wall, the two nerve networks inside it, the pacemaker cells that set its rhythm, and what happens when part of the network never forms (Hirschsprung disease). It also explains why the popular nickname "second brain" is useful but misleading, and it introduces the two tools you will use in every chapter: the Hype Meter and the six questions for reading a gut-brain claim.

Concepts Covered

1. Digestive Tract
2. Gut Wall Layers
3. Smooth Muscle
4. Central Nervous System
5. Peripheral Nervous System
6. Autonomic Nervous System
7. Gut-Brain Axis
8. Enteric Nervous System
9. Myenteric Plexus
10. Submucosal Plexus
11. Enteric Neuron
12. Enteric Glia
13. Interstitial Cells of Cajal
14. Peristalsis
15. Peristaltic Reflex
16. Migrating Motor Complex
17. ENS Neuron Count

18. Neural Crest
19. Hirschsprung Disease
20. Second Brain Metaphor
21. Hype Meter
22. Evidence Grade

Prerequisites

None. Just one year of high school biology. If you want a refresher on neurons, see From Neuron to Bedside.

Hi, I'm Vee, your vagus nerve guide



I'm a vagus nerve fiber, the long line that carries messages between your gut and your brainstem, so I'll carry this book's messages too. You'll see me when there's a key idea to think about, a tip, a common mistake to dodge, a hard part worth pushing through, and a win to celebrate. Almost every gut-brain claim you'll see online starts with "your gut has its own brain," and you're about to find out how true that is. Let's check what the gut is really telling the brain!

1.1 Does Riya's Gut Have a Mind of Its Own?

Riya was 14 when she was diagnosed with Crohn's disease, after months of belly pain, diarrhea, weight loss, and a tiredness that sleep never fixed. On her first day back at Lakeview High, a friend asked what was wrong, and Riya, who did not feel like explaining inflammation in the hallway, said, "My gut has a mind of its own." Her friend laughed. Riya did too. But later, waiting for her first appointment with her pediatric gastroenterologist, Dr. Alvarez, she wondered whether the joke was closer to the truth than she thought. Does the gut actually make its own decisions? (Riya is a fictional student who appears throughout this book.)

In 1755, the Swiss scientist Albrecht von Haller noticed that a piece of intestine removed from an animal's body kept making its wave-like movements, even though it was no longer connected to the brain. Scientists still see the same thing today: cut every nerve to the brain and spinal cord, and a segment of intestine keeps pushing its contents along. So the gut really does run some of its own business. Whether that counts as a "mind" is what this chapter sorts out.

Riya's best friend Sam has his own version of the question. Sam runs cross-country, and before big races his stomach flips and churns. Is that his gut acting alone, or his brain talking to his gut? We'll start on that in Chapter 2. For now, remember two facts: the gut has its own local network, and it is also wired to the brain.

If you're going through this

If you have a gut condition, you have probably had to explain your body to people at bad moments, like Riya in that hallway. You don't owe anyone a full medical explanation. A short line such as "I have a health condition and might need the restroom" is enough, and your care team or school nurse can help you set up a plan with teachers. Learning how your gut works won't fix everything, but many people find it makes their body feel less mysterious and easier to talk about.

1.2 The Digestive Tract: A Muscular Tube With Layers

Before we meet the gut's neurons, we need to know what they live in. Picture a long garden hose that runs through your body. Now imagine that the hose is not plastic but made of several sleeves stacked inside each other, and that one of those sleeves is muscle that can squeeze. That is a good first picture of your digestive tract.

The **digestive tract** is the continuous tube that food travels through, from the mouth through the throat, esophagus, stomach, small intestine, and large intestine (colon) to the anus. Doctors also call it the gastrointestinal (GI) tract. In a living adult it is about 7.6 meters (25 feet) long, coiled up inside the abdomen, according to the open textbook *Anatomy and Physiology 2e* from OpenStax.

Along most of its length, the wall of the tube has the same basic structure. The **gut wall layers** are four tissue layers stacked from the inside (the open space where food travels, called the lumen) to the outside:

1. **Mucosa.** The inner lining that touches food, with cells that absorb nutrients, make mucus, and release hormones, plus immune tissue.
2. **Submucosa.** Loose connective tissue with blood vessels, lymph vessels, and glands. One of the gut's two nerve networks lives here.
3. **Muscularis.** The muscle layer that squeezes. In the small intestine it has an inner layer of muscle wrapped in rings (circular muscle) and an outer layer running the long way (longitudinal muscle). The second nerve network sits between them.
4. **Serosa.** A thin, slippery outer covering for the parts of the tract inside the abdomen.

The table below summarizes the four layers and adds which of the gut's two nerve networks each one holds. (We'll define those networks in Section 1.4.)

Layer (inside to outside)	What it's made of	What it mainly does	Nerve network found here
Mucosa	Lining cells, mucus cells, hormone cells, immune tissue	Absorbs, secretes, senses what is in the gut	None of its own (nerve endings reach it)

Layer (inside to outside)	What it's made of	What it mainly does	Nerve network found here
Submucosa	Connective tissue, blood and lymph vessels	Supports the lining, carries blood	Submucosal plexus
Muscularis	Two sheets of smooth muscle	Mixes and moves contents	Myenteric plexus (between the sheets)
Serosa	Thin connective tissue covering	Lets the gut slide against nearby organs	None

The muscle in the muscularis is a special kind. **Smooth muscle** is muscle made of small, spindle-shaped cells that contract slowly and can stay partly contracted for a long time, without you deciding to move it. You can choose to bend your elbow, but you can't choose to squeeze your small intestine. (A few spots, such as the mouth, throat, upper esophagus, and the outer ring of muscle at the anus, use skeletal muscle instead, which is why you control swallowing.) When the circular muscle contracts, it pinches the tube narrower, like a hand closing around a toothpaste tube.

Coordinate that squeeze into a traveling wave, and you can push food a long way. The rest of this chapter is about who does the coordinating.

1.3 Two Nervous Systems, One Body

You already know the basic layout of the nervous system from biology class, so here is a quick refresher. Neurons are cells that carry electrical signals and pass messages to other cells at junctions called synapses. The **central nervous system** (CNS) is the brain and spinal cord, the body's main processing center. The **peripheral nervous system** (PNS) is everything outside the brain and spinal cord: the nerves that branch out to your skin, muscles, and organs, and the clusters of nerve cell bodies (ganglia) along the way. For a deeper review of neurons and brain anatomy, see From Neuron to Bedside, Chapter 1 and Chapter 4.

Part of the peripheral nervous system runs the body's background jobs, the ones you never think about, like heart rate, sweating, and digestion. The **autonomic nervous system** is this automatic, involuntary part of the nervous system that controls internal organs, glands, and smooth muscle. Textbooks usually describe two branches:

- The **sympathetic** branch, often called "fight or flight." When it is active, it tends to slow digestion: secretions drop and gut muscle movement is held back.
- The **parasympathetic** branch, often called "rest and digest." When it is active, it tends to speed digestion up. The vagus nerve (Vee's home) is its biggest gut connection.

Early in the 1900s, the British physiologist John Newport Langley proposed that the autonomic nervous system actually has *three* divisions: sympathetic, parasympathetic, and a third one inside the gut wall. Many reviews still describe it that way, and that third division is the star of this chapter.

Think of a city. The brain and spinal cord are city hall. The sympathetic and parasympathetic nerves are phone lines to each neighborhood. And the gut has its own neighborhood council that handles local problems, like clearing a blocked street, without calling city hall. City hall can call in and change priorities, and the council sends reports back, but routine work needs no permission.

All of these pieces talk to each other. The **gut-brain axis** is the two-way communication system linking the gut (its nervous system, hormones, immune cells, and microbes) with the brain. Signals travel both up and down, and nerves are only one route; later chapters cover hormones, immune messengers, and chemicals made by gut microbes. This chapter is about the local network at the gut end of the conversation.

1.4 Meet the Enteric Nervous System

The **enteric nervous system** (ENS) is the network of neurons and support cells built into the wall of the digestive tract, running from the esophagus to the anus. ("Enteric" comes from a Greek word for intestine.) A 2020 review by Spencer and Hu describes the gut as the only internal organ that evolved its own complete nervous system, one that can work fully independently of input from the brain and spinal cord.

Imagine two layers of fishing net wrapped around the garden hose from Section 1.2, one tucked under the lining and one sandwiched inside the muscle. Each knot is a small cluster of nerve cell bodies called a ganglion, and the strings are bundles of nerve fibers.

The **myenteric plexus** (also called Auerbach's plexus) is the outer network of ganglia, located between the circular and longitudinal muscle layers. It runs the whole length of the gut and mainly controls movement: the rhythm and strength of contractions. ("Plexus" means a network of nerves.)

The **submucosal plexus** (also called Meissner's plexus) is the inner network of ganglia, located in the submucosa just under the lining. It is found mainly in the small and large intestines. It mostly controls what the lining does, such as releasing fluid and mucus, and it helps sense what is in the gut.

So many new names



I know, "myenteric" and "submucosal" look like a lot on day one. Here's my trick: **my**enteric sits in the **m**uscle and runs **m**ovement, while **sub**mucosal sits **sub** (under) the mucosa and runs the lining.

An **enteric neuron** is a nerve cell whose cell body sits in the gut wall, inside one of the ENS ganglia. A 2020 review by Fleming and colleagues says the ENS contains up to 20 types of neurons, in three big job categories:

- **Sensory neurons** (scientists call them intrinsic primary afferent neurons) detect stretch of the gut wall and chemicals in the gut.
- **Interneurons** pass signals up and down the gut, connecting sensory neurons to motor neurons.
- **Motor neurons** send signals to muscle and glands. Some are excitatory and make muscle contract, often using the chemical messenger acetylcholine. Others are inhibitory and make muscle relax, often using nitric oxide.

That is everything you need to build a reflex, all inside the gut wall. Hold on to that idea for Section 1.7.

The second kind of cell is the support crew. **Enteric glia** are non-neuron cells in the ENS that surround and support enteric neurons and help regulate gut function. Scientists once thought glia were just packing material, but a 2021 review by Seguella and Gulbransen says that view has been refuted. Enteric glia appear to help regulate gut reflexes, the gut lining's barrier, and immune responses, though much of that evidence comes from animals. They also outnumber enteric neurons; one review estimates roughly 2 to 3 glia per neuron, a rough figure from a single source.

1.5 How Many Neurons Are in Your Gut?

This is the number wellness posts love to quote. The **ENS neuron count** is the estimated total number of neurons in the human enteric nervous system. The careful version of the fact, used throughout this book, is this:

> The enteric nervous system contains hundreds of millions of neurons, about 400 to 600 million by common estimates, roughly as many as the spinal cord.

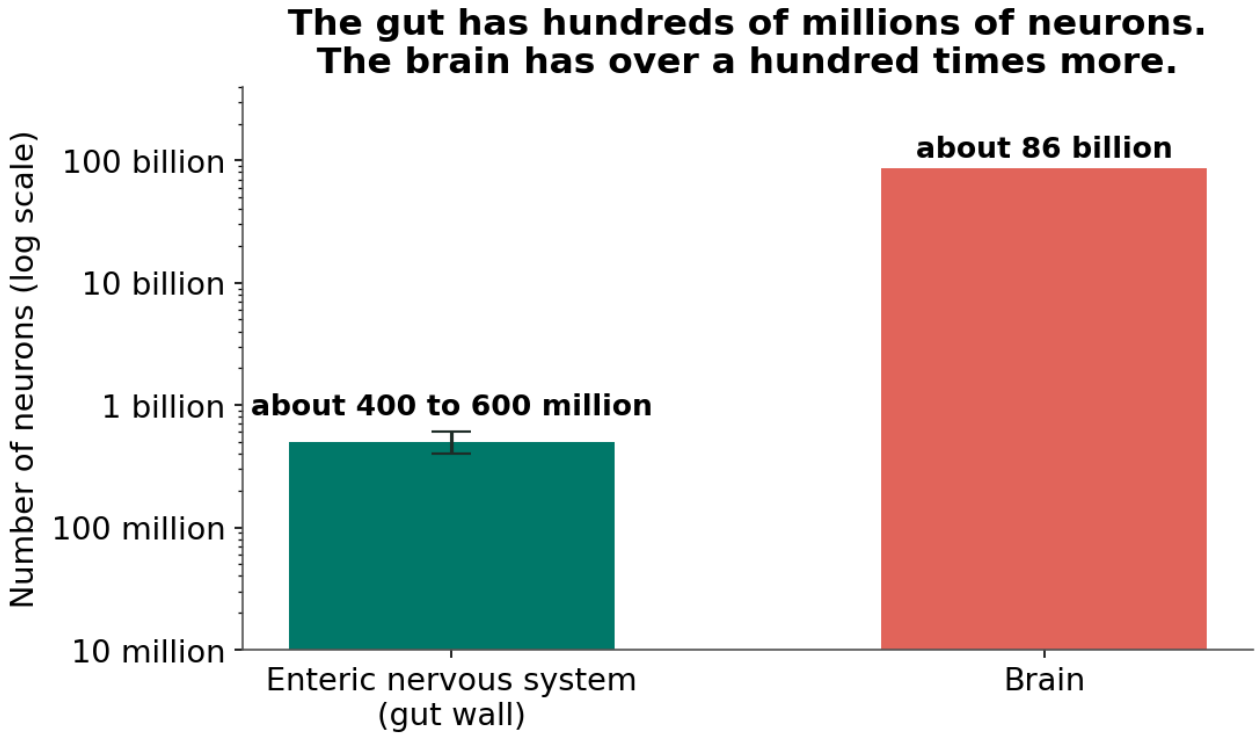
Why "estimates"? Nobody can count every neuron in a gut several meters long, so scientists count small samples and multiply up, and different methods give different answers. A 2016 review by Rao and Gershon says "more than 100 million," a 2019 review by Schneider, Wright, and Heuckeroth says "more than 500 million," and the 2020 Fleming review says "approximately 400 to 600 million." Some textbooks, including OpenStax, give about 100 million. The order of magnitude is solid; the exact figure is not.

Now compare that with the brain. In 2009, a team including Frederico Azevedo and Suzana Herculano-Houzel counted cells in adult male human brains using a cell-counting method called the isotropic fractionator. They found about 86 billion neurons on average. Here is the comparison side by side:

Structure	Approximate number of neurons	Source
Enteric nervous system (gut wall)	About 400 to 600 million (estimates vary)	Fleming 2020; Schneider 2019; Rao and Gershon 2016
Spinal cord	Roughly similar to the ENS	Fleming 2020; Rao and Gershon 2016

Structure	Approximate number of neurons	Source
Brain	About 86 billion	Azevedo et al. 2009

Do the math: 86 billion divided by 500 million is about 170, so the brain has well over a hundred times more neurons. Still, Rao and Gershon note that the ENS has more neurons than all the body's other peripheral ganglia combined, and far more than the number of vagus nerve fibers carrying commands down to the gut. The brain doesn't have enough wires to micromanage the gut, so the gut has to handle much of its own control.



Source: Fleming et al. 2020; Schneider et al. 2019; Azevedo et al. 2009. The scale is logarithmic: each step up is ten times bigger.

Big for a nerve net, small for a brain



When you see "your gut has millions of neurons," both parts can be true: it's a huge number for a nerve network, and a tiny one next to your brain's 86 billion. Always ask, "Compared with what?"

1.6 The Gut's Pacemakers: Interstitial Cells of Cajal

Your heart has pacemaker cells that set its beat. Your gut has something similar. Think of a drummer in a marching band: the drummer doesn't decide where the band marches, but the beat tells everyone when to step.

Interstitial cells of Cajal (ICC) are specialized cells in the gut's muscle layers that generate rhythmic electrical signals, called slow waves, which set the timing of smooth muscle contractions. They are named after Santiago Ramón y Cajal, a Spanish scientist and Nobel Prize winner famous for his studies of nerve cells. ICC are neither neurons nor muscle cells, but they are electrically connected to the muscle.

A slow wave is a gentle, repeating rise and fall in the electrical charge of muscle cells that spreads from the ICC and sets the timing of contractions. ICC also help pass signals from enteric motor neurons to the muscle, so how strongly the muscle squeezes depends on the neurons too. ICC set the beat; the enteric neurons decide which steps happen.

How do scientists know ICC are the pacemakers? ICC carry a receptor protein called Kit on their surface. In 1994, Ward, Sanders, and colleagues studied mice with mutations in the gene for Kit. These mice had very few ICC in the myenteric region of the small intestine, and recordings from their intestinal muscle showed that the electrical slow waves were missing. Normal sibling mice always had slow waves, and a 1995 study by Huizinga and colleagues found the same link. The mutant muscles still responded when enteric nerves were stimulated, so nerve control can develop without ICC.

Notice the kind of evidence. These were **mouse** studies, but they were **experiments that tested cause**: change one gene, lose the cells, lose the rhythm. Human disease data later supported the same picture, so "ICC are gut pacemakers" rates as Strong.

There is a catch. The Spencer and Hu review notes that in some experimental animals, the small intestine's pacemaker ICC can be removed without wrecking normal function, while mice that lack an ENS cannot push food along and die. The beat helps, but the band can't march without the enteric neurons.

1.7 Peristalsis: How Food Gets Pushed

Squeeze the bottom of a toothpaste tube and slide your fingers toward the cap. Now imagine the tube could do that by itself, sensing where the paste is and squeezing just behind it. That's what your intestine does.

Peristalsis is a wave of muscle contraction that travels along the digestive tract and pushes its contents forward, toward the anus. (The intestine also makes mixing movements, but peristalsis is how food makes forward progress.)

What triggers each wave? The **peristaltic reflex** is a local reflex of the enteric nervous system in which stretching of the gut wall causes the muscle behind the stretched spot (on the mouth side) to contract and the muscle ahead of it (on the anus side) to relax. In 1899, the physiologists Bayliss and Starling, working with loops of dog intestine, summarized it as a "law of the intestine": local stimulation produces excitation above the stimulated spot and inhibition below it. During World War I, the scientist Paul Trendelenburg studied

isolated segments of intestine, completely cut off from the brain and spinal cord, and gave the response the name we still use today: the peristaltic reflex.

Here is the reflex step by step, using the three neuron types from Section 1.4:

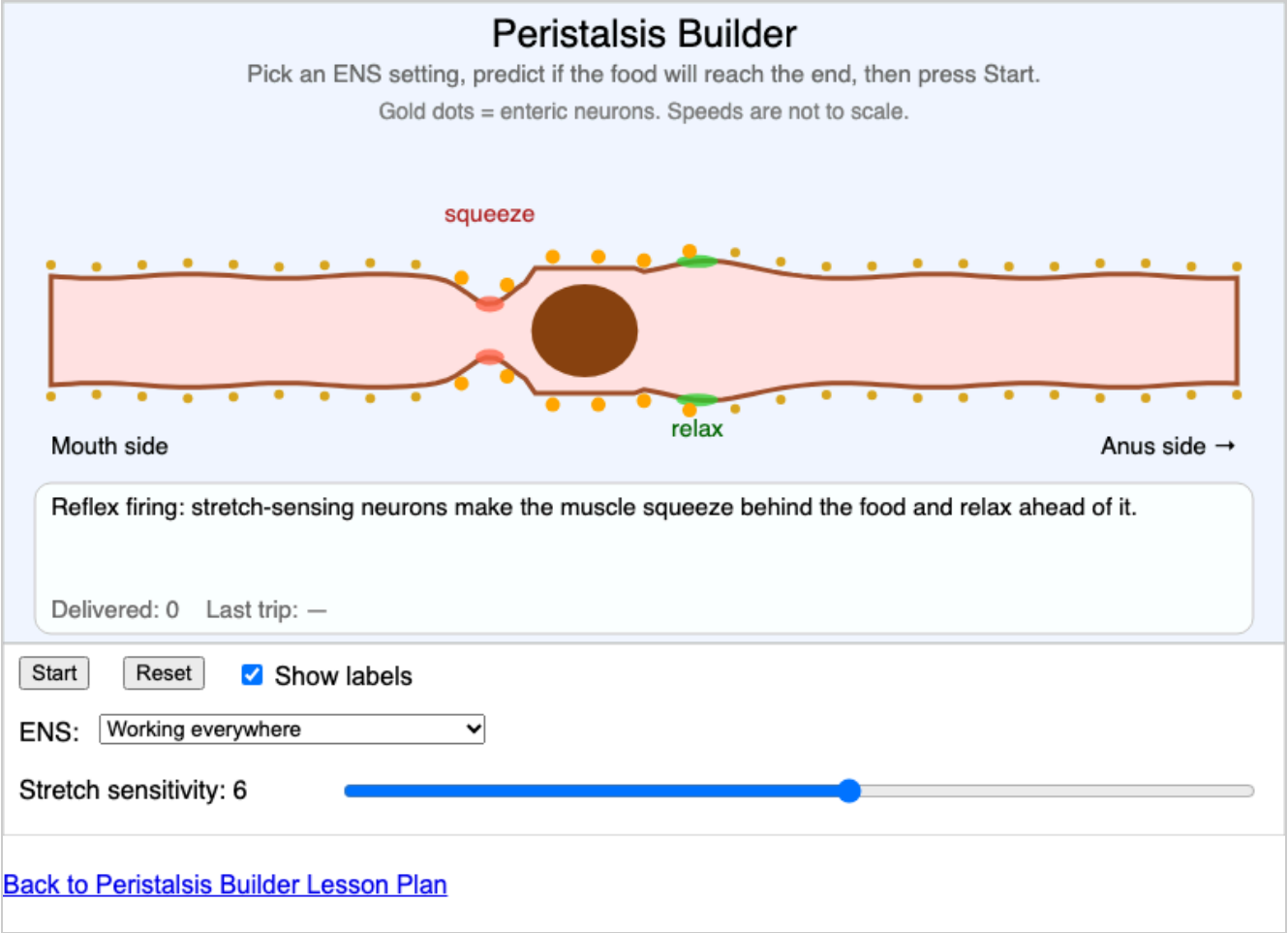
1. **Stretch.** A ball of food (doctors call it a bolus) stretches the gut wall.
2. **Sense.** Stretch-sensing enteric neurons in that spot fire.
3. **Relay.** Interneurons carry the signal in two directions: back toward the mouth side and forward toward the anus side.
4. **Squeeze behind.** On the mouth side, excitatory motor neurons tell the circular muscle to contract. The tube pinches closed behind the bolus.
5. **Relax ahead.** On the anus side, inhibitory motor neurons tell the circular muscle to relax. The tube opens up in front of the bolus.
6. **Repeat.** The bolus moves into the relaxed section, stretches a new spot, and the cycle starts again a little farther along.

Step 5 is as important as step 4: if the tube ahead stays clamped shut, squeezing behind the food just builds pressure. That is exactly what goes wrong in Hirschsprung disease. And notice what is *not* on the list: the brain. It can speed the process up or slow it down, but the reflex itself is local.

One correction to an older idea: many textbooks said serotonin released from the gut lining triggers peristalsis. The Spencer and Hu review says evidence, mostly from animals, now suggests it is *not required*, although it can change how the waves behave. (More on gut serotonin in Chapter 5.)

In the simulation below, "stretch sensitivity" means how easily the stretch-sensing neurons fire, the red zone is contracting circular muscle behind the bolus, and the green zone is relaxing muscle ahead of it.

Diagram: Peristalsis Builder



Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch01-peristalsis-builder/main.html

Open the Peristalsis Builder fullscreen

MicroSim specification: Peristalsis Builder

Type: microsim **sim-id:** ch01-peristalsis-builder
Library: p5.js
Status: Implemented
Bloom Level: Understand
Bloom Verb: explain
Learning Objective: The learner will explain how the peristaltic reflex moves a bolus as a local enteric circuit (stretch, then contraction behind and relaxation ahead) and predict why the bolus stalls where enteric neurons are missing.

Canvas: 400 px drawing area plus 120 px controls (iframe 522 px); responsive to about 380 px wide.

Controls: Start/Pause, Reset, Show labels; ENS select (Working everywhere; Missing at the end, like Hirschsprung; Switched off everywhere); Stretch sensitivity slider (1 to 10, step 1, default 6, arbitrary units).

Rules: The reflex fires when the stretch signal (5 x sensitivity / 6) is >= 3.5, so sensitivity 1 to 4 gives no reflex and 5 to 10 does; speed rises with sensitivity. The bolus advances only if the segment ahead has enteric neurons and can relax. A no-neuron segment stays narrowed (contracted). With no ENS, pacemaker ripples continue but do not move the bolus. Material backs up behind a blockage.

Feedback: A status panel names the state (paused, firing, below trigger, stalled, no ENS, delivered) and shows deliveries and last trip time (illustrative seconds).

Provenance: Section 1.7 (Spencer and Hu 2020; Bayliss and Starling 1899); contracted no-neuron segment (Heuckeroth 2018). All numbers are illustrative.

Start with the ENS **working everywhere** and press Start. Watch the red "squeeze" zone chase the bolus while the green "relax" zone opens the way ahead; the gold neuron dots light up only near the food. Then drag the stretch sensitivity down to 4 or lower. The signal falls below the trigger level, so the reflex never fires. Raise it again and compare trip times at 6 and 10.

Now predict: if the last part of the tube has no enteric neurons, where will the food stop? Choose **Missing at the end (like Hirschsprung)** and test it. The bolus stalls at the edge of the no-neuron zone, which stays squeezed because it has no inhibitory neurons, and the tube behind it swells. Finally, try **Switched off everywhere**: the pacemaker ripples continue, but they can't move anything.

What this model leaves out

- A real gut is several meters long with many boluses, mixing movements, and fluid, not one ball in a straight tube.
- Real reflexes travel through chains of interneurons and dozens of neuron types; the sim shows only "sense, squeeze, relax."
- The brain, spinal cord, and vagus nerve can speed up or slow down peristalsis; the sim leaves out all outside nerve input and hormones.
- Speeds, stretch values, and the trigger level are made-up teaching numbers, not measurements.
- In real Hirschsprung disease, the length of the no-neuron segment varies from child to child, and the swelling builds over days, not seconds.

1.8 Between Meals: The Migrating Motor Complex

What does the gut do when you haven't eaten for a while? It cleans house.

The **migrating motor complex** (MMC) is a repeating pattern of strong contractions that sweeps slowly along the stomach and small intestine during fasting, between meals. Picture a street sweeper that comes through on a schedule when there's no traffic, pushing leftover debris onward toward the large intestine.

A 2012 review by Deloose and colleagues describes the MMC as a cyclic pattern that occurs during fasting and is interrupted by eating. It is divided into phases, and the most active phase (phase III) is a burst of strong contractions that starts in the lower stomach or upper small intestine and travels downstream. In humans, phase III contractions come back roughly every 90 to 120 minutes, according to a 2012 review by Toku Takahashi. Because problems with the MMC have been linked to an overgrowth of bacteria in the small intestine, older papers nicknamed it the gut's "housekeeper."

The MMC also gives us more evidence for the ENS's independence. The Deloose review notes that cutting the vagus nerve (a surgery called vagotomy) stops the MMC's motor activity in the stomach but leaves the repeating activity in the small intestine intact.

Hormones help control the MMC too: one gut hormone, motilin, rises and falls with its phases, and some recent research suggests these contractions may help signal hunger, an idea still being tested. The key point: even with no food to push, the ENS keeps its own timetable.

1.9 Where Enteric Neurons Come From: The Neural Crest

Every neuron in your ENS started somewhere else. Early in development, the embryo forms a tube of tissue that will become the brain and spinal cord. Along the edges of that tube, a special group of cells breaks away and travels through the body. The **neural crest** is this group of embryonic cells that forms at the edge of the

developing neural tube and migrates throughout the embryo, giving rise to many cell types, including the neurons and glia of the enteric nervous system.

Nearly all enteric neurons and glia come from the neural crest, and most come from one region of it, called the vagal neural crest, located in the lower part of the developing hindbrain, near the junction between brain and spinal cord. (A smaller group from the lower end of the neural tube, the sacral neural crest, adds cells mainly to the end of the colon.) A 2017 review by Nagy and Goldstein describes how these cells enter the top of the gut in about the fourth week of development in humans and then migrate down the gut tube from top to bottom, colonizing the entire length of the gut. In bird and rodent embryos, the leading edge of these migrating cells moves at about 40 micrometers per hour.

Think of it like settlers spreading across a continent from one coast: the last region to be reached is the far end. That's why, if the migration falls short, the part left without neurons is almost always the *end* of the bowel.

The trip depends on chemical signals. Nagy and Goldstein call RET, a receptor protein on the migrating cells, critically important for ENS development, and changes in the RET gene and several others raise the chance that migration falls short.

1.10 When the Network Is Missing: Hirschsprung Disease

Hirschsprung disease is a condition present from birth in which enteric neurons are missing from the last part of the large intestine, so that segment cannot relax and push stool forward, causing a blockage. A 2018 review by Heuckeroth puts it plainly: when the ENS is missing, there are no nerve-driven pushing movements, and the bowel stays contracted. Without neurons, the gut doesn't go limp, as many people guess. It stays squeezed, because the inhibitory neurons that would tell it to relax aren't there. Stool backs up behind it, just like in the sim's "missing at the end" setting.

The no-neuron stretch always starts at the rectum, but its length varies: NIDDK says that in about 80% of children it is short (the rectum and sometimes the lowest part of the colon), while in about 5% to 10% nerve cells are missing from the whole large intestine, and sometimes part of the small intestine too.

According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), about 1 in 5,000 newborns has Hirschsprung disease. The condition is named after Harald Hirschsprung, a Danish children's doctor who presented two cases at a medical conference in Berlin in 1886 and published his description in 1888. Some babies show signs of a blocked intestine soon after birth, such as not passing a first stool within 48 hours, green or brown vomit, and a swollen belly. Other children are diagnosed later because of long-lasting constipation that doesn't get better with usual treatments.

Hirschsprung disease is clear human evidence that the ENS is not optional. These children have a working brain, spinal cord, and vagus nerves; missing the local network in one segment is enough to stop the bowel.

For families

If a baby or child in your family has Hirschsprung disease, it helps to know where it comes from: nerve cells in the gut didn't finish developing before birth, and certain genes raise the chance. Many parents wonder whether they caused it, and that is a good question to bring to the care team, who can explain what is known for your child. After surgery, many children do well, but some have ongoing issues such as constipation or trouble with bowel control, so regular follow-up with the care team matters. Siblings may feel left out during hospital stays; a simple explanation like "the end of the baby's gut didn't get its nerve cells, and the doctors fixed the part that wasn't working" can help them feel included.

1.11 "Second Brain": A Useful Nickname, a Misleading Claim

By now you can see why people call the ENS a "brain in your belly": it is large, has its own sensory and motor circuits, and can run without the brain. In 1998, the Columbia University scientist Michael D. Gershon published a popular book called *The Second Brain*, and the nickname spread. Researchers still use it. A 2019 scientific review is titled "Unexpected roles for the second brain."

The **second brain metaphor** is the comparison of the enteric nervous system to a brain, which highlights that it is large, complex, and able to work independently, but which can mislead people into thinking the gut thinks, feels, or decides like the brain does. Here is where the comparison holds up and where it breaks down:

What the ENS does (supported)	What the "second brain" phrase can wrongly suggest (not supported)
Senses stretch and chemicals in the gut	That the gut has thoughts or feelings
Runs local reflexes like peristalsis	That the gut makes decisions or plans
Controls secretion, mixing, and blood flow in the gut wall	That "gut instinct" comes from gut neurons thinking on their own
Works without input from the brain	That the ENS is equal to the brain
Sends signals to the brain and receives signals from it	That the gut has more neurons than the brain

None of the research reviews used for this chapter describe the ENS as thinking, reasoning, or feeling. They describe movement, secretion, blood flow, and barrier and immune roles. A sophisticated reflex network is impressive enough without exaggeration.

So what about "gut feelings," like Sam's pre-race butterflies? Those feelings are real, but you feel them with your *brain*. Signals from the gut travel up to the brain, mostly through the vagus nerve and spinal nerves, and the brain turns them into sensations like nausea, fullness, or that fluttery feeling. The brain also sends signals back down that change how the gut behaves. That two-way traffic is the subject of Chapters 2 and 7. The gut senses and reports; it doesn't think.

Watch the word "thinks"



The structure fact ("your gut has its own nervous system") is rock solid, but the leap to "your gut thinks and feels" is not. When a post slides from the first claim to the second, that slide is exactly where hype sneaks in.

1.12 The Hype Meter: Grading Gut-Brain Claims

The gut-brain axis is real science, and also one of the most oversold topics in wellness. A finding in a few mice can become "this supplement cures anxiety" by the time it reaches your feed.

The **Hype Meter** is this book's four-level scale for grading how well the evidence supports a popular gut-brain claim, from Strong to Moderate to Preliminary to Hype. When we apply it, we give a claim an **evidence grade**, the rating that summarizes how strong and how direct the scientific support for a specific claim is, as it is actually stated.

Strong means consistent evidence in people, usually from large or repeated studies, randomized trials (experiments where people are assigned to groups by chance), or well-established physiology. **Moderate** means good animal evidence plus some human evidence, or a strong, repeated link in people whose cause is still unclear. **Preliminary** means small, early, short, or mostly animal studies. **Hype** means a popular claim the evidence does not support, or one that stretches a real finding far beyond what it shows. The table below summarizes the four grades.

Grade	Typical evidence	What it means for you
Strong	Repeated human studies, trials, textbook physiology	Treat as established (still not personal medical advice)
Moderate	Animals plus some humans, or a solid link without a proven cause	Probably real in part; details still being worked out
Preliminary	Few, small, short, or animal-only studies	Worth watching; don't act on it yet

Grade	Typical evidence	What it means for you
Hype	Popular claim not backed by evidence	Be skeptical, especially if someone is selling something

Two rules make the Hype Meter work. First, **grade the claim as stated**, not the topic. "Your gut has its own nervous system" and "your gut thinks" start from the same fact but get very different grades. Second, **grades can change** as new studies come out; this book logs changes on its Accuracy page. And a "Strong" grade for a treatment never means it is right for you personally. That is a conversation for you and your doctor. Here are three claims you're likely to hear about this chapter's topic.

Hype Meter: "Your gut can move food without your brain"

Strong | Moderate | Preliminary | Hype

Verdict: Strong. Since 1755, scientists have watched isolated pieces of intestine, cut off from the brain and spinal cord, keep making propulsive movements, and modern experiments on animal intestine show the same thing. The small intestine keeps its between-meal contraction cycles after the vagus nerve is cut, and children with Hirschsprung disease show that losing the local neurons, not the brain connection, is what stops the bowel. **What would change the grade:** Very little. It rests on more than two centuries of consistent experiments plus human disease evidence.

Hype Meter: "Your gut is a second brain that thinks and feels"

Strong | Moderate | Preliminary | Hype

Verdict: Hype. The part about the gut having a large, independent nervous system is Strong. But the research describes the ENS running reflexes for movement, secretion, blood flow, and immune and barrier roles, not thinking, planning, or feeling. Gut sensations become feelings only when signals reach the brain. **What would change the grade:** Repeated, well-designed studies showing that enteric circuits by themselves do something more like choosing or learning than reflexes, in animals and then in people, could move the "thinks" part up to Preliminary.

Hype Meter: "Your gut has more neurons than your brain"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. The ENS has about 400 to 600 million neurons by common estimates, roughly as many as the spinal cord. The brain has about 86 billion, well over a hundred times more, based on cell counts in adult human brains. **What would change the grade:** Nothing realistic. Even the highest gut estimates are far below the brain count.

1.13 How to Read a Gut-Brain Claim: Six Questions

A grade is only as good as the reasoning behind it, so every chapter applies the same six questions to at least one real study. You can use them on any health headline, ad, or post.

1. **Mouse or human?** Many gut-brain findings come from mice, including mice raised with no microbes at all. Mouse results often don't carry over to people.
2. **Correlation or cause?** Two things happening together is a correlation, not proof that one causes the other. The arrow might point the other way, or a third factor might explain both. Showing cause usually takes an experiment that changes one thing on purpose and compares with a group where nothing changed.
3. **How many?** Small studies swing wildly by chance. A result in 12 people or 8 mice is a hint, not an answer.
4. **How long?** A two-week change might not last, and a long-term harm might not show up yet.
5. **Who paid for it?** Funding doesn't make a study wrong, but it's worth knowing who benefits. Good papers include a funding and conflict-of-interest statement.
6. **Is something being sold?** If a claim ends with a product, a test kit, a diet plan, or a program, read it twice as carefully.

Use the questions on good studies too



These questions aren't only for spotting bad science. Use them on excellent studies too, because even a great study answers only the question it actually asked.

Let's practice on a real, high-quality study from this chapter's topic. In 2020, a team at the Broad Institute of MIT and Harvard (first author Drokhlyansky, with senior authors Regev and Xavier) published an atlas of enteric neurons in the journal *Cell*. They developed new methods to read which genes are active in single cells. In mice, they profiled 1,187,535 cell nuclei, which included 5,068 neurons from the small intestine and colon. In humans, they profiled 436,202 nuclei from colon tissue and recovered 1,445 neurons. The human tissue came from the healthy-looking edges of colon sections removed during surgery from 16 people with colon cancer,

aged 35 to 90. The team found dozens of distinct types of enteric neurons, including 21 neuron subsets in one mouse dataset.

How to read a gut-brain claim: the 2020 enteric neuron atlas

Question	This study
Mouse or human?	Both. Most of the data came from mice (including 29 mice for one detailed dataset), plus colon tissue from 16 human patients.
Correlation or cause?	Neither, really. This is a descriptive map: it catalogs which genes each neuron type uses. It can suggest what neurons might do, but it doesn't test cause.
How many?	Very large numbers of cells (over 1.6 million nuclei) but only 1,445 human neurons from 16 people, all of whom had colon cancer surgery.
How long?	A snapshot. Each sample was taken once, so it can't show changes in one person over time (though the mouse data compared ages and times of day).
Who paid for it?	The paper lists the Klarman Cell Observatory, the Howard Hughes Medical Institute, several NIH grants, the Manton Foundation, the Helmsley Charitable Trust, the Crohn's and Colitis Foundation, and others.
Is something being sold?	No product is sold to the public. However, several authors are co-inventors on a patent application covering the methods, and some hold equity in or work for biotech or drug companies, as the paper's conflict-of-interest statement discloses.

The conclusion: this is careful, valuable research supporting the idea that the ENS has many neuron types. It does **not** show that any neuron type causes a disease, and the human tissue came from adults with cancer, who might not represent healthy teens. The patent and company ties don't make the findings wrong; they are facts a careful reader notes.

At the Bedside: A Newborn Who Can't Pass Stool

Meet the patient (fictional)

Mateo is a 2-day-old baby in a hospital newborn nursery. His parents notice that he hasn't had his first bowel movement, even though other babies born the same day have. By his second day, his belly looks round and tight, he isn't feeding well, and he vomits green fluid.

What the doctor checks: The newborn team takes a family history, examines Mateo's swollen belly, and notes that he has not passed a first stool within 48 hours of birth, a key warning sign. Imaging, such as a contrast enema (a liquid that shows up on X-rays, put in through the rectum), shows the shape of the large intestine. The test that confirms the diagnosis is a rectal biopsy: tiny pieces of rectal tissue examined under a microscope.

Connecting the signals: No stool plus a swollen belly means a blockage, but nothing is physically stuck. The pathologist finds no ganglion cells (the enteric neuron clusters) in the submucosal layer of the biopsy samples, the layer a rectal biopsy usually reaches. In Hirschsprung disease, the neurons are missing from both nerve networks in the affected segment. Without enteric neurons, the last part of his colon can't relax to let stool through.

Diagnosis: Hirschsprung disease.

Why it happens: Before Mateo was born, the neural crest cells that should have colonized his gut from top to bottom did not finish colonizing the end of his colon. The segment without enteric neurons stays contracted, so the peristaltic reflex in the healthy gut above it pushes stool into a section that never opens. That is the "missing at the end" setting of the Peristalsis Builder.

The mind-body side: Mateo can't explain how he feels, but his parents carry a lot of fear and guilt in the first days, and many ask whether they caused this. The care team explains what is known: the nerve cells in the gut didn't finish developing before birth, and genes play a role. Neonatal nurses, surgeons, and social workers may all help the family understand the surgery, hold and feed their baby when possible, and plan for life at home. As children grow up, bowel control problems can affect confidence at school, and care teams can connect families with support.

Treatment today: The main treatment is surgery called a pull-through procedure. The surgeon removes the part of the large intestine that is missing nerve cells and connects the healthy part to the anus. Some children first need ostomy surgery, which creates a usually temporary opening (a stoma) on the belly for stool to leave while the intestine heals. According to NIDDK, children most often feel better after surgery, but about half may have ongoing problems such as constipation, trouble with bowel control, or a serious gut inflammation called Hirschsprung-associated enterocolitis, which needs hospital care right away.

What's new in research: In 2016, a team led by Fattahi and Studer reported in *Nature* that they could grow early enteric nervous system cells from human stem cells in the lab. When they transplanted these cells into the colons of mice with a Hirschsprung-like condition, the cells spread into the gut and the mice were more likely to survive, although the researchers said the reason was unclear. **Evidence grade: Preliminary.** These are mouse and lab results; cell therapy for Hirschsprung disease is experimental and not a standard treatment. In 2025, a Massachusetts General Hospital team led by pediatric surgeon Allan Goldstein reported that its mouse studies of a therapy using a patient's own gut nerve stem cells were largely complete and that it planned to ask the FDA to begin a first trial in people. As of October 2026, we found no cell therapy trial for Hirschsprung disease registered on ClinicalTrials.gov, and no results in children have been reported.

Your turn: reason through a variation

A 4-year-old has had constipation for years that hasn't improved with the usual medicines, and his belly is often swollen. His parents read about Hirschsprung disease and ask, "Isn't that only in newborns?" How would you reason about this?

Answer: No. Many children with Hirschsprung disease show symptoms as newborns, but not all. NIDDK says about half are diagnosed in the first year of life and about 80% by age 7. Children diagnosed later often have a short segment without neurons and milder symptoms. Constipation that doesn't respond to usual treatment is one sign in older children. Many other things cause constipation, so only the care team can sort it out, and a rectal biopsy is still the test that confirms or rules out Hirschsprung disease.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: The brain has to send a command for every movement of the gut.
Reality: The enteric nervous system runs the peristaltic reflex locally. Pieces of intestine cut off from the brain keep pushing their contents along. The brain adjusts gut activity but isn't needed for the basic reflex.

Myth: The gut has more neurons than the brain.
Reality: The ENS has about 400 to 600 million neurons by common estimates, roughly as many as the spinal cord. The brain has about 86 billion, well over a hundred times more.

Myth: "Second brain" means the gut is equal to the brain and can think or feel.
Reality: The ENS is a large, independent reflex network. It senses and controls movement, secretion, and blood flow in the gut. Sensations like butterflies or nausea are created by the brain from signals the gut sends up.

Myth: If part of the gut has no neurons, it just goes limp.
Reality: In Hirschsprung disease, the segment without enteric neurons stays contracted because there are no inhibitory neurons to relax it. That is why it blocks stool instead of letting it slide through.

Myth: The pacemaker cells of the gut can move food on their own.
Reality: Interstitial cells of Cajal set the rhythm of muscle activity, but animals without an enteric nervous system can't push food along, even when their pacemaker cells are present. The beat needs the neurons.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Your gut has more neurons than your brain. That's why you should always trust your gut over your head!"

Grade: Hype. The first sentence is false: the ENS has about 400 to 600 million neurons, while the brain has about 86 billion. The second doesn't follow even from true facts: the ENS runs reflexes, not decisions, and "gut feelings" are sensations your brain creates from gut signals. A careful version would say: "Your gut has its own network of hundreds of millions of neurons that runs digestion locally and sends signals to your brain."

2. Predict: Riya's cousin had surgery years ago in which the vagus nerve to his stomach was cut. Riya asks Dr. Alvarez whether food can still move through his small intestine. What would you predict, and why?

Food should still move through his small intestine, because the peristaltic reflex is run by the ENS inside the gut wall. Research on the migrating motor complex also shows that after vagotomy, the stomach part of the between-meal pattern stops, but the small intestine's repeating activity continues. His stomach's movements might change, since the vagus nerve plays a bigger role there.

3. Explain: A newborn with Hirschsprung disease has a swollen belly. Use the peristaltic reflex to explain why the belly swells above the part of the colon without neurons.

In the healthy gut above the missing segment, stool stretches the wall, sensory enteric neurons fire, and the muscle squeezes behind the stool as it should. But the segment ahead has no inhibitory motor neurons, so it can't relax and stays contracted. Stool and gas keep getting pushed toward a section that never opens, so they pile up and stretch the gut above it, which makes the belly swell.

4. Apply: In a lab, a scientist places a small balloon inside an isolated segment of guinea pig intestine and inflates it. The segment has no connection to the brain or spinal cord. What will happen to the muscle on each side of the balloon?

The balloon stretches the gut wall, which triggers the peristaltic reflex. On the mouth side of the balloon, the circular muscle should contract; on the anus side, it should relax. This is Bayliss and Starling's "law of the intestine." It works because sensory neurons, interneurons, and motor neurons are all inside the gut wall, so no brain connection is needed.

5. Read the data. In the 2020 enteric neuron atlas (Drokhlyansky et al., *Cell*), researchers profiled cell nuclei from gut tissue and counted how many turned out to be neurons. Here are their numbers:

Sample	Nuclei profiled	Neurons recovered
Mouse small intestine and colon	1,187,535	5,068

Sample	Nuclei profiled	Neurons recovered
Human colon (16 patients)	436,202	1,445

5. What does this data show, and what can't it show?

It shows that neurons are a tiny fraction of the cells in gut tissue: about $5{,}068 \div 1{,}187{,}535 \approx 0.4\%$ in the mouse samples and about $1{,}445 \div 436{,}202 \approx 0.3\%$ in the human samples. That's why the team needed special methods to find them. It can't give the total neuron count of a whole gut, because these were small samples processed to enrich and filter cells, not to count everything. It also can't show cause or say much about healthy teens, since the human tissue came from 16 adults having cancer surgery. A helpful follow-up: a similar atlas from a wider range of healthy donors, including younger people.

Exercises

Remember

1. Name the four layers of the gut wall, from the inside out.

Answer

Mucosa, submucosa, muscularis, and serosa.

1. Where is the myenteric plexus located, and what does it mainly control?

Answer

It sits between the circular and longitudinal muscle layers of the gut wall and mainly controls gut movement (the rhythm and strength of contractions).

Understand

1. Explain why relaxation of the muscle ahead of a bolus is as important as contraction behind it.

Answer

Squeezing behind the bolus only moves it forward if the tube ahead opens. If the muscle ahead stays contracted, pressure builds but the bolus can't advance, which is what happens at the no-neuron segment in Hirschsprung disease.

1. In your own words, explain the difference between the ENS neuron count being "solid in order of magnitude" and "uncertain in exact number."

Answer

Scientists agree the ENS has hundreds of millions of neurons, not thousands and not billions. But because they count small samples and scale up with different methods, estimates range from more than 100 million to about 600 million, so no single exact number is reliable.

Apply

1. A wellness video says, "Your gut is your second brain, so it knows what foods your body needs." Use the second brain metaphor table in Section 1.11 to identify which part of this claim is supported and which part is not, and give it an evidence grade.
2. Using the MicroSim, record the trip time at stretch sensitivity 4, 6, 8, and 10 (press Reset before each run; if the food never arrives, record "no trip"). Describe the pattern, then explain what "stretch sensitivity" represents in real enteric neurons and why the model's numbers can't be compared to a real gut.

Analyze

1. Compare the evidence from the 1994 Kit mutant mouse experiments with the evidence from children with Hirschsprung disease. For each, answer two of the six questions (mouse or human, and correlation or cause). Which tells you more about humans, and which is better at showing cause?
2. Riya's Crohn's disease affects the end of her small intestine and part of her colon, and her enteric nervous system is present. A newborn with Hirschsprung disease is missing enteric neurons in the end of the colon. Analyze how the cause of a bowel problem differs between "the nerve network is missing" and "the gut is inflamed," and why this difference matters for treatment.

Evaluate

1. Some scientists think the "second brain" nickname helps the public appreciate the ENS; others think it causes more confusion than it's worth. Write a one-paragraph judgment: should this textbook keep using the phrase? Support your position with at least two pieces of evidence from this chapter.

2. Evaluate this headline: "Scientists map 21 types of gut neurons, showing your gut is smarter than you think." Use at least four of the six questions and the claim-box in Section 1.13 to decide what grade the headline deserves.

Create

1. Design a simple experiment, using isolated segments of animal intestine, that would test whether a particular drug blocks the relaxation part of the peristaltic reflex but not the contraction part. Describe your groups, what you would measure, and the result that would support your hypothesis.
2. Create a short social-media post (under 280 characters) that correctly explains what the enteric nervous system does, uses the "second brain" phrase responsibly, and would earn a Strong grade on the Hype Meter.

Key Takeaways

- The digestive tract is a muscular tube with four wall layers; its smooth muscle squeezes without conscious control.
- The enteric nervous system, built into the gut wall, has two networks: the myenteric plexus (mainly movement) and the submucosal plexus (mainly the lining). It contains hundreds of millions of neurons, about 400 to 600 million by common estimates, roughly as many as the spinal cord, and far fewer than the brain's 86 billion.
- The peristaltic reflex is a local circuit: stretch triggers contraction behind the food and relaxation ahead of it, with no command from the brain needed. Between meals, the migrating motor complex sweeps the stomach and small intestine.
- Interstitial cells of Cajal set the gut's rhythm, but propulsion needs enteric neurons.
- Enteric neurons come from neural crest cells that migrate down the gut before birth. When they don't reach the end, the result is Hirschsprung disease, in which the segment without neurons stays contracted and blocks the bowel.
- "Second brain" is a useful nickname for a large, independent reflex network, but claims that the gut thinks, feels, or outnumbers the brain are Hype.
- The Hype Meter (Strong, Moderate, Preliminary, Hype) and the six questions (mouse or human, correlation or cause, how many, how long, who paid, is something being sold) are your tools for every claim in this book.

You built a gut from the ground up!



You now know what's really in that "brain in your belly" and how to grade claims about it. Next, in Chapter 2, we'll ride the vagus nerve, my home highway, to see how the gut and brain actually send messages to each other.

Quiz: The Brain in Your Belly (and Why That Phrase Is Misleading)

Test your understanding of Chapter 1. Choose the best answer, then click **Show Answer** to check.

Question 1

Where is the myenteric plexus located?

A. In the mucosa, right under the cells that touch food

B. Between the circular and longitudinal muscle layers of the gut wall

C. In the brainstem, where the vagus nerve begins

D. In the serosa, on the outside surface of the gut

Show Answer

The correct answer is **B**. The myenteric (Auerbach's) plexus sits between the two smooth muscle sheets and mainly controls gut movement. Option A describes roughly where the submucosal plexus is (just under the lining, in the submucosa), which is an easy mix-up.

Concept Tested: Myenteric Plexus **Bloom's Level:** Remember

Question 2

Which statement about the number of neurons in the human enteric nervous system matches the evidence in this chapter?

A. It has about 86 billion neurons, the same as the brain.

B. It has more neurons than the brain, which is why it is called the second brain.

C. It has only a few thousand neurons, too few to run reflexes.

D. It has hundreds of millions of neurons, about 400 to 600 million by common estimates.

Show Answer

The correct answer is **D**. Common estimates put the ENS at about 400 to 600 million neurons, roughly as many as the spinal cord. About 86 billion is the brain's count, so options A and B confuse the two; the brain has well over a hundred times more neurons than the gut.

Concept Tested: ENS Neuron Count **Bloom's Level:** Remember

Question 3

What are interstitial cells of Cajal best known for?

A. Generating the slow electrical waves that set the timing of gut muscle contractions

B. Sensing stretch and triggering the peristaltic reflex by themselves

C. Making most of the body's antibodies in the gut lining

D. Carrying signals from the gut up the vagus nerve to the brain

Show Answer

The correct answer is **A**. ICC are the gut's pacemaker cells: they generate slow waves that time smooth muscle contractions. Option B is tempting, but stretch is sensed by enteric sensory neurons, and animals without an ENS can't push food along even when ICC are present.

Concept Tested: Interstitial Cells of Cajal **Bloom's Level:** Remember

---

Question 4

Why does the muscle need to relax *ahead* of a ball of food during the peristaltic reflex?

A. Relaxation ahead signals the brain that food has arrived.

B. Relaxation ahead lets the pacemaker cells reset their rhythm.

C. Relaxation ahead opens the tube so the squeeze behind can actually move the food forward.

D. Relaxation ahead is not needed; contraction behind the food is enough.

Show Answer

The correct answer is **C**. Contraction behind the food only pushes it forward if the segment ahead opens up. Option D is the key misconception: if the segment ahead stays contracted, as in Hirschsprung disease, squeezing behind just builds pressure and the food stalls.

Concept Tested: Peristaltic Reflex **Bloom's Level:** Understand

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Question 5

In Hirschsprung disease, what happens to the segment of bowel that has no enteric neurons?

A. It goes limp and floppy, so stool slides through too fast.

B. It stays contracted and cannot relax, so stool backs up behind it.

C. It becomes inflamed because immune cells attack the neurons.

D. It is controlled directly by the vagus nerve instead, so it works normally.

Show Answer

The correct answer is **B**. Without enteric neurons, there are no inhibitory neurons to relax the muscle, so the segment stays contracted and causes a functional blockage. Option A is a common guess, but losing the neurons removes the "relax" signal, not the muscle's tone.

Concept Tested: Hirschsprung Disease **Bloom's Level:** Understand

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Question 6

Why is the end of the bowel the part left without neurons when ENS development falls short?

A. Neural crest cells enter the top of the gut and migrate downward, so the far end is colonized last.

B. The end of the bowel destroys neural crest cells as they arrive.

C. Neurons at the end of the bowel are made by the brain and arrive after birth.

D. The end of the bowel does not need neurons in healthy people.

Show Answer

The correct answer is **A**. Most enteric neurons come from the vagal neural crest, enter the top of the gut, and colonize it from top to bottom, so a migration that stops short leaves the far end empty. Option D is wrong because Hirschsprung disease shows that the end of the bowel does need its neurons.

Concept Tested: Neural Crest **Bloom's Level:** Understand

Question 7

A post says: "Your gut is a second brain that thinks and feels." Using the Hype Meter, what grade does this claim as stated deserve?

A. Strong, because the gut really has its own nervous system

B. Moderate, because the gut has many neurons but scientists are unsure what they do

C. Preliminary, because only mouse studies have looked at gut neurons

D. Hype, because the ENS runs reflexes, and no evidence shows it thinks or feels

Show Answer

The correct answer is **D**. The Hype Meter grades the claim as stated. The structure fact is Strong, but the leap to "thinks and feels" is not supported: the research describes reflexes for movement, secretion, and blood flow. Option A grades the true starting fact instead of the actual claim.

Concept Tested: Hype Meter **Bloom's Level:** Apply

Question 8

Riya's friend learns that after a vagotomy (cutting the vagus nerve), the stomach part of the migrating motor complex stops but the small intestine's repeating activity continues. What is the best conclusion?

A. The vagus nerve controls all gut movement, so the small intestine must be getting signals another way.

B. The migrating motor complex happens only after meals.

C. The small intestine can keep its between-meal contraction pattern without the vagus nerve, which fits local control by the ENS.

D. The stomach has more enteric neurons than the small intestine.

Show Answer

The correct answer is **C**. The small intestine keeps its own schedule without the vagus nerve, which supports the idea that the enteric nervous system can run gut patterns locally. Option A assumes the brain must be in charge, which is exactly what the result argues against; option B is wrong because the MMC happens during fasting and is interrupted by eating.

Concept Tested: Migrating Motor Complex **Bloom's Level:** Apply

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Question 9

The 2020 enteric neuron atlas profiled colon tissue from 16 adults having colon cancer surgery and recovered 1,445 human neurons. Which limitation matters most if you want to apply its human findings to healthy teens?

A. The study was paid for by a supplement company.

B. The human tissue came from a small number of adults with cancer, who may differ from healthy teens.

C. The study used only mice, so it says nothing about humans.

D. The study was a randomized trial, so it can't describe cell types.

Show Answer

The correct answer is **B**. The human samples came from 16 adults aged 35 to 90 having cancer surgery, so they may not represent healthy young people. Option C is wrong because the study included human tissue, and option A is wrong because its funders were mainly research institutes, foundations, and NIH grants.

Concept Tested: Evidence Grade **Bloom's Level:** Analyze

Question 10

In 1994, mice with mutations in the gene for Kit had very few interstitial cells of Cajal and no slow waves, while their normal siblings had slow waves. What does this experiment show, and what is its main limit?

A. It shows only a correlation in humans, and its limit is that it was too large.

B. It proves that the brain sets the gut's rhythm, and its limit is that it was short.

C. It shows that enteric neurons are not needed for movement, and its limit is funding.

D. It tests cause (change one gene, lose the cells, lose the rhythm), and its limit is that it was done in mice.

Show Answer

The correct answer is **D**. Changing one gene and seeing the cells and rhythm disappear is an experiment that points to cause, but it was done in mice, so it needed human evidence before the claim could be graded Strong. Option C overreaches: the mutant mice's muscles still responded to enteric nerves, and other work shows the ENS is needed for propulsion.

Concept Tested: Interstitial Cells of Cajal **Bloom's Level:** Analyze

Chapter 2: The Vagus Highway

Summary

The gut runs its own reflexes, but it also stays in constant contact with the brain. This chapter follows the main nerve line between them, the vagus nerve, from the gut wall up to the brainstem and back down again. You will learn why most vagus traffic travels upward (gut to brain), how the brainstem sends commands back down to the stomach, how special sensor cells in the gut lining release hormones such as CCK and GLP-1 that tell you when you are full, and why the vagus is not the only wire, since spinal nerves carry many gut sensations too. Along the way, you will grade popular claims about "resetting" your vagus nerve and learn what happens when surgeons cut it.

Concepts Covered

1. Cranial Nerve
2. Brainstem
3. Sympathetic Nervous System
4. Parasympathetic Nervous System
5. Vagus Nerve
6. Afferent Signal
7. Efferent Signal
8. Nodose Ganglion
9. Nucleus Tractus Solitarius
10. Dorsal Motor Nucleus
11. Spinal Afferent Nerve
12. Interoception
13. Enteroendocrine Cell
14. Neuropod Cell
15. Gut Hormone
16. Cholecystokinin
17. GLP-1
18. Satiety Signal

19. Vagal Tone
20. Vagotomy

Prerequisites

- Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading), especially the autonomic nervous system, the gut-brain axis, and the enteric nervous system.
- If you want a refresher on how neurons pass signals, see From Neuron to Bedside, Chapter 3.

Welcome to my home highway



This chapter is personal for me, because the vagus nerve is where I live. Every time you feel full, queasy, or fluttery before a big moment, signals are racing along nerves like me. Social media is full of tricks that promise to "hack" or "reset" your vagus nerve, so knowing how it really works will help you sort the solid science from the sales pitch.

2.1 How Does Sam's Brain Know What His Stomach Is Doing?

It's the morning of the regional cross-country meet, and Sam is standing at the start line. His stomach feels tight and a little sick, even though he ate only a small breakfast hours ago. Two days later, on the day of his chemistry final, he sits down to lunch, takes a few bites of a sandwich, and suddenly feels full, as if his stomach has shrunk. (Sam is a fictional student who appears throughout this book. He has IBS with mixed bowel habits and test anxiety.)

Sam's experiences raise a simple question with a long answer: how does the brain know what the gut is doing? And how does the brain, in turn, change what the gut does? In Chapter 1 you learned that the gut runs its own local reflexes. But Sam doesn't feel his gut with his gut. He feels it with his brain. Something has to carry the news upward, and something has to carry instructions back down. This chapter is about those messengers.

2.2 A Highway With Lanes in Both Directions

Picture a long highway connecting a big city to a busy port. Trucks drive in both directions. Some carry reports from the port to the city: how many ships just arrived, whether the docks are crowded, whether there's a fire. Others carry orders from the city to the port: open another dock, slow down unloading, send extra workers. If you stood on a bridge over that highway and counted, you might find that most trucks are heading toward the city, because the city needs a steady stream of information to make good decisions.

Your body has a highway like this between your gut (the port) and your brain (the city). Scientists use two words for the two directions:

- An **afferent signal** is a signal carried by nerve fibers *toward* the central nervous system (brain or spinal cord), usually sensory information from the body. A trick to remember it: **a**fferent **a**rrives.
- An **efferent signal** is a signal carried by nerve fibers *away from* the central nervous system, out to muscles, glands, or organs, usually a command. Remember: **e**fferent **e**xits.

The same nerve can carry both kinds of fibers, packed side by side in one bundle like lanes on a highway. Each individual fiber carries signals in only one direction, but the bundle as a whole is a two-way road.

Ask which way the traffic flows



Whenever you read about a gut-brain nerve, ask, "Is this signal arriving at the brain or exiting from it?" Afferent arrives, efferent exits. Mixing them up is a common mistake people make about me.

2.3 Cranial Nerves and the Brainstem

Most nerves in your body connect to the spinal cord. A special set connects directly to the brain instead. A **cranial nerve** is one of the twelve nerves (on each side of the head) that connect directly to the brain rather than the spinal cord, numbered with Roman numerals I through XII. According to the open textbook *Anatomy and Physiology 2e* from OpenStax, four of the twelve are "mixed" nerves that carry both sensory and motor fibers. The tenth is the one this chapter is about.

Most cranial nerves connect to the lowest part of the brain. The **brainstem** is the stalk of brain tissue that connects the rest of the brain to the spinal cord. It has three parts: the midbrain, the pons, and the medulla, with the medulla at the bottom, continuous with the spinal cord. OpenStax notes that the pons and medulla together help regulate the heart and breathing. (For a full tour of brain anatomy, see From Neuron to Bedside, Chapter 4.)

Now meet the nerve. The **vagus nerve** (cranial nerve X) is a long, mixed nerve that runs from the medulla of the brainstem down through the neck and chest into the abdomen, carrying both sensory and motor fibers to and from organs such as the heart, lungs, and digestive tract. A StatPearls review by Kenny and Bordoni calls it the longest cranial nerve. "Vagus" comes from a Latin word meaning wandering, a good name for a nerve that wanders so far from the head. There is one vagus nerve on each side of the body, and in the abdomen its branches reach the stomach, the intestines, the liver, and the pancreas.

2.4 Two Branches of the Autonomic Nervous System

Chapter 1 introduced the autonomic nervous system, the automatic part of the nervous system that runs your organs. Now we need its two main branches in more detail, because the vagus belongs to one of them.

The **sympathetic nervous system** is the branch of the autonomic nervous system that prepares the body for action or stress, often called "fight or flight." Its nerves leave the spinal cord in the chest and lower back. When it is active, your heart speeds up, your airways open, and digestion slows: the gut makes less fluid, and its muscle movements are held back. That makes sense if you are running from danger. Blood and energy go to your muscles, not to your lunch.

The **parasympathetic nervous system** is the branch of the autonomic nervous system that supports "rest and digest" activities, such as slowing the heart and speeding up digestion. Its nerves leave from two places: the brainstem (traveling in cranial nerves) and the lowest part of the spinal cord. The vagus nerve is the biggest parasympathetic nerve by far. A 2018 review by Bonaz and colleagues calls it the principal component of the parasympathetic nervous system.

Feature	Sympathetic	Parasympathetic
Nickname	Fight or flight	Rest and digest
Where its nerves leave the central nervous system	Spinal cord in the chest and lower back	Brainstem (cranial nerves, including the vagus) and the lowest spinal cord
Heart rate	Speeds up	Slows down
Digestion	Slows down	Speeds up
Main gut connection	Spinal nerves to the gut	Vagus nerve (plus pelvic nerves for the last part of the colon)

These nicknames are useful, but don't overlearn them. OpenStax points out that "fight or flight" is incomplete, and the two branches usually work together like a gas pedal and a brake. And the vagus nerve is not a "calm button." Most of its fibers, as you're about to see, are sensors.

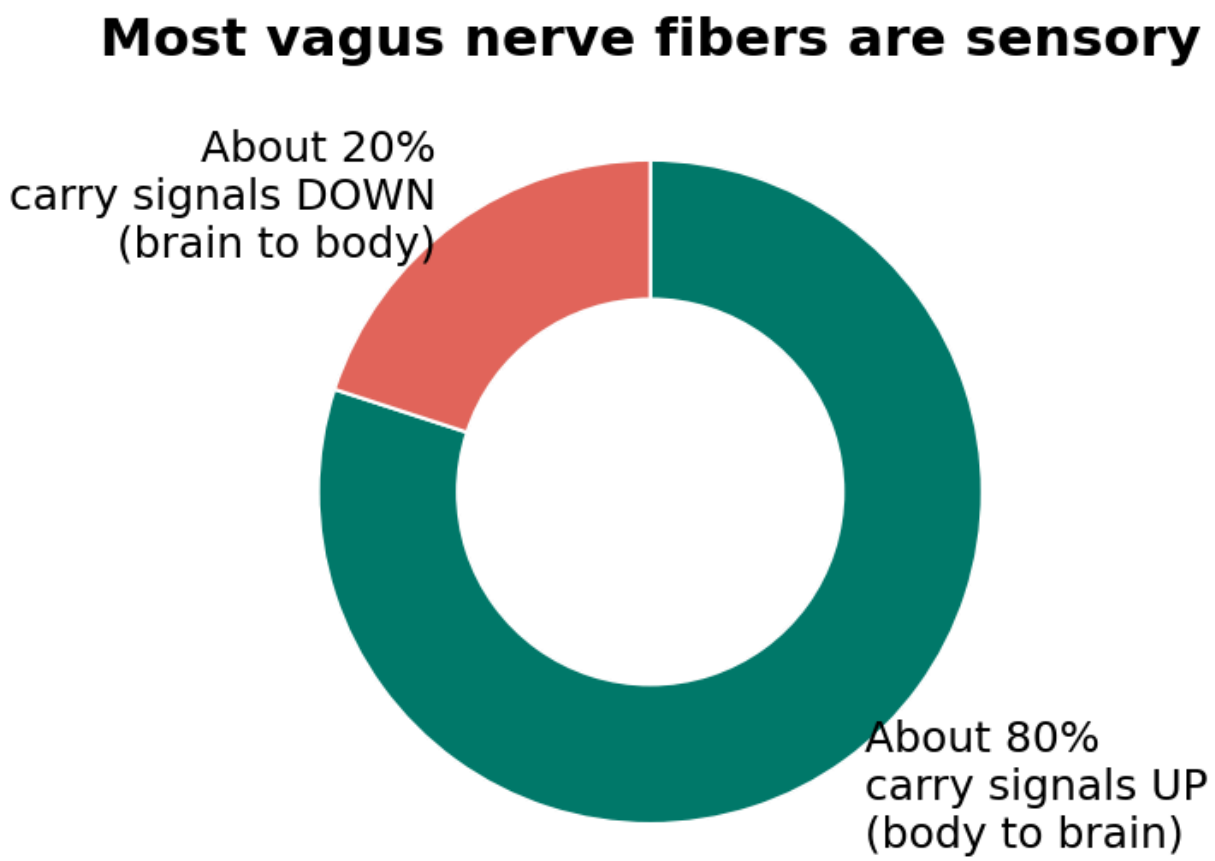
2.5 How Many Lanes Go Up? The 80% Figure

The most surprising fact about the vagus nerve is how it splits its traffic. People often describe it as the brain's way of controlling the gut, a cable of commands. But when scientists count the fibers in the nerve, most of them carry information the other way.

The careful version of the fact, used throughout this book, is this:

> Most vagus nerve fibers carry signals from the body to the brain. Classic fiber counts in animals put the figure at about 80%.

A 2022 review by Prescott and Liberles in the journal *Neuron* says most vagal neurons (about 80%) are sensory, and it traces that figure to classic animal fiber counts: a 1937 study of the vagus nerve in cats by Foley and DuBois. (This book relies on the review's report of that old study; we did not open the 1937 paper itself.) The 2018 Bonaz review describes the vagus as 80% afferent and 20% efferent fibers. So of every ten fibers in the nerve, roughly eight report to the brain and two carry commands down.



Source: classic animal fiber counts, as summarized by Prescott and Liberles 2022 and Bonaz et al. 2018. The split is approximate and varies between studies and species.

But notice the words "classic" and "in animals." Nobody has done a modern, complete fiber count of the human vagus nerve that settles the exact number. And one careful study suggests the split varies. In 1990, Prechtl and Powley counted every fiber in cross-sections of the abdominal vagus in rats using an electron microscope. They concluded that motor (efferent) fibers might make up over a quarter of the fibers there, a higher share than the widely accepted estimates. The precise share depends on the species, which branch of the nerve you count, and how you count.

What doesn't change is the big picture: most vagus traffic is sensory. The brain spends most of this cable on listening.

Hype Meter: "80% of your vagus nerve sends signals up to your brain"

Strong	**Moderate**	Preliminary	Hype

Verdict: Moderate. That most vagus fibers are sensory is well supported by anatomy reviews. The specific "80%" comes from old fiber counts in cats, and a careful 1990 rat study found that motor fibers in the abdominal vagus may be over a quarter of the total. The general claim ("most vagus fibers carry signals to the brain") would rate Strong; the exact percentage, applied to humans, is an approximation. **What would change the grade:** A modern, careful fiber count of human vagus nerves, branch by branch, could confirm or revise the number.

2.6 The Route Up: From the Gut Wall to the Brainstem

Let's follow one afferent signal from the stomach to the brain. Imagine Sam's lunch stretching the wall of his stomach.

Step 1: The sensor. The ending of a vagal sensory fiber sits in the stomach wall. When the wall stretches, the ending fires electrical signals. Different vagal sensory neurons detect different things. In a 2016 study in mice, Williams and colleagues used genetic tools to show that one group of vagal sensory neurons responded to stretching of the stomach and intestine, while a different group responded to nutrients in the gut.

Step 2: The cell body. Sensory neurons have their cell bodies (the part that holds the nucleus) clustered in a lump outside the brain. The **nodose ganglion** is the cluster of cell bodies of vagal sensory neurons, located on the vagus nerve just below the skull in the neck; it is also called the inferior vagal ganglion. ("Nodose" means knotted, because it looks like a knot on the nerve.) Each nodose neuron has a long fiber reaching down to the organ and another fiber reaching up into the brainstem, so a signal passes straight through on its way up. A smaller group of vagal sensory neurons sits in a second cluster just above it, the jugular ganglion. In mice the two are fused into one, but in humans they are separate.

Step 3: The first stop in the brain. The **nucleus tractus solitarius** (NTS), also called the nucleus of the solitary tract, is a cluster of neurons in the medulla of the brainstem that receives incoming sensory signals from the vagus nerve and passes them on to other brain areas. The Prescott and Liberles review says nodose neurons send their signals mainly to the NTS, and that vagal fibers release the neurotransmitter glutamate there to excite NTS neurons. (Much of this wiring was mapped in animals, but the general layout is well established.)

From the NTS, information spreads to brain areas that control breathing and heart rate, hunger and stress, and conscious feeling. The NTS is like the city's central post office: it sorts the incoming mail and forwards it.

2.7 The Route Down: The Dorsal Motor Nucleus and the Vago-Vagal Reflex

Now follow the traffic the other way. The **dorsal motor nucleus** of the vagus (DMV) is a cluster of neurons in the medulla, next to the NTS, whose fibers travel down the vagus nerve to carry efferent (motor) signals to the stomach and intestines. These fibers don't usually connect directly to the gut's muscle. Instead, they connect to neurons of the enteric nervous system, which then carry out the order. Remember the neighborhood council from Chapter 1? The DMV is city hall calling the council, not doing the street repairs itself.

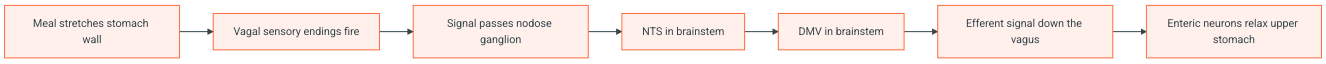
Two nuclei, side by side



NTS and DMV look like alphabet soup at first, but there's a pattern: the NTS is where my sensory fibers **arrive**, and the DMV is where my motor fibers **depart**. They sit right next to each other in the brainstem, so a message can come in and a reply can go out almost immediately.

Because the NTS and DMV are neighbors and are wired to each other, the brainstem can run a loop: a sensory signal comes up the vagus, and a motor command goes back down the same nerve. Scientists call this a vago-vagal reflex (the vagus talking to itself through the brainstem). A 2016 review by Travagli and Anselmi describes these brainstem circuits as connecting incoming vagal fibers, NTS neurons, and outgoing fibers from the DMV, and notes that they are highly changeable, even shifting after stress.

Here's a real example. When a meal stretches your stomach, a 2013 review by Farré and Tack explains, stretch-sensing receptors trigger the upper stomach to relax and make room, a response called gastric accommodation, partly through vago-vagal reflexes. Later, when nutrients reach the first part of the small intestine, signals traveling mainly through vago-vagal reflexes slow down how fast the stomach empties. Your stomach is like an expandable backpack, and the vagus helps unzip the extra pocket when the load arrives.



Notice what this loop does *not* need: your conscious mind. The brainstem handles it.

2.8 The Other Wires: Spinal Afferent Nerves

The vagus is not *the* gut-brain connection. A 2013 review by Brookes and colleagues describes gut sensory neurons as organized into three separate pathways to the central nervous system: the vagal pathway, plus two pathways that enter the spinal cord, one in the middle of the back (thoracolumbar) and one lower down (lumbosacral).

A **spinal afferent nerve** is a sensory nerve fiber that carries signals from an organ, such as the gut, to the spinal cord rather than directly to the brainstem, with its cell body in a ganglion beside the spinal cord. From the spinal cord, signals travel up to the brain. A 2018 review by Brierley, Hibberd, and Spencer explains that spinal afferents reaching the colon and rectum come in many types that can detect gut contents, gentle and strong stretching, and chemicals released during inflammation. They give rise to sensations of discomfort, bloating, urgency, and pain.

Here's how the two wiring systems compare in general terms:

	Vagal afferents	Spinal afferents
Path to the brain	Directly to the brainstem (NTS)	Into the spinal cord, then up to the brain
Cell bodies	Nodose and jugular ganglia, in the neck	Ganglia beside the spinal cord
Typical messages	Stretch, nutrients, gut hormones, some inflammation signals; fullness and nausea	Stretch, inflammation, injury; discomfort, urgency, and much of gut pain
Gut coverage	Most of the digestive tract	Whole gut, including the end of the colon and rectum

When someone has gut pain, much of that message can travel through spinal routes, which is one reason cutting or stimulating the vagus doesn't simply switch gut feelings on or off. Chapter 8 explores pain pathways in detail.

2.9 Interoception: Sensing the Inside of Your Body

You have senses that point outward: sight, hearing, touch, taste, smell. You also have senses that point inward. You can tell when you are hungry, full, thirsty, out of breath, or when your heart is pounding. Scientists have a word for this.

Interoception is the process by which the nervous system senses, interprets, and combines signals from inside the body, such as fullness, nausea, heartbeat, and breathing, creating a moment-to-moment map of the body's internal state. A 2018 expert roadmap led by Sahib Khalsa describes interoception as working at both conscious and unconscious levels, and notes that problems with interoception are increasingly recognized in conditions such as anxiety disorders, mood disorders, and eating disorders. That doesn't mean interoception causes those conditions; researchers are still working out how the pieces fit.

Vagal and spinal afferents are the raw data for gut interoception. Much of it never reaches awareness, but some does, like Sam's tight stomach at the start line. The 2013 Brookes review notes that gut sensory neurons give rise to sensations such as fullness, bloating, nausea, discomfort, urgency, and pain.

Riya knows one of those sensations well. During her Crohn's flares, she often feels nauseated, even when she hasn't eaten anything unusual. (Riya is a fictional 16-year-old with Crohn's disease who appears throughout this book.) At one visit she asks her gastroenterologist, Dr. Alvarez, why inflammation in her intestine would make her feel sick to her stomach. Dr. Alvarez explains that the inflamed gut releases chemicals that can switch on sensory nerve endings. Reviews of animal research describe some gut sensory fibers that stay quiet

until inflammatory chemicals turn them on. Some of these signals travel up the vagus to the NTS, which sits among the brainstem circuits that a 2014 review by Babic and Browning describes as central to nausea and vomiting. "Your gut isn't imagining it, and neither are you," Dr. Alvarez says. "The nausea is real information traveling a real pathway."

If you're going through this

If your gut condition makes you feel nauseated, full, or uncomfortable at unpredictable times, those feelings are real signals traveling real nerves, not something you're making up. It's worth keeping track of when they happen and telling your care team, because nausea and early fullness can point to things they can treat. You don't have to "push through" a meal or a class just to prove you're fine; it's okay to ask your school nurse or counselor for a plan.

2.10 Sensor Cells in the Gut Lining

The nerve endings in the gut wall don't sit right at the surface where food touches. Between them and your lunch is a single layer of lining cells. So how do nerves find out what's in the gut? Part of the answer is a special group of sensor cells scattered through that lining.

Think of them as smoke detectors spaced along a hallway, each sampling the air and sounding an alarm when it finds something.

An **enteroendocrine cell** is a hormone-releasing sensor cell scattered among the lining cells of the stomach and intestines, which detects nutrients and other substances in the gut and responds by releasing hormones and other signals. ("Entero" means intestine and "endocrine" means hormone-releasing.) They are rare: the Prescott and Liberles review says they make up about 1% of intestinal lining cells. But because the gut lining is enormous, that still adds up to a lot of sensors.

What do they release? A **gut hormone** is a chemical messenger made by cells of the digestive tract, mostly enteroendocrine cells, that travels through the blood or acts on nearby nerves to influence digestion, appetite, and blood sugar. A 2019 review by Gribble and Reimann describes gut hormones as made by scattered cells along the intestinal lining that signal nutrient absorption, food intake, and blood sugar control. Some travel through the bloodstream; others act locally on the vagal sensory endings next door.

For decades, scientists thought enteroendocrine cells talked to nerves only this indirect way, by releasing hormones that drift over to nearby nerve endings. Then a lab at Duke University found something surprising. The lab had noticed that some enteroendocrine cells in mice have a long, foot-like extension, which they named a neuropod. In 2015, Bohórquez and colleagues reported that neuropods reach out and directly contact nerves.

In 2018, the same lab, with first author Melanie Kaelberer, published a study in *Science* showing that in mice, these cells form actual synapses with vagal sensory neurons and pass signals to them using glutamate, a fast neurotransmitter. A **neuropod cell** is an enteroendocrine cell that forms synapse-like connections with nerve

fibers and sends signals to them quickly, so far described mostly in mice. The team reported that in lab dishes where these gut cells were grown together with vagal neurons, connected neurons responded within milliseconds. A 2022 follow-up study by Buchanan and colleagues found that in mice, neuropod cells help the animals tell real sugar from artificial sweetener, and the preference for sugar depended on the cells' glutamate signaling.

Let's apply the six questions from Chapter 1, Section 1.13 to the 2018 study.

How to read a gut-brain claim: the 2018 neuropod cell study

Question	This study
Mouse or human?	Mouse. The experiments used genetically modified mice, mouse gut tissue grown in dishes (organoids), and mouse vagal neurons. No human tissue was tested for synapses.
Correlation or cause?	Mostly cause, in mice. The team switched the gut cells on and off with light (optogenetics) and blocked glutamate receptors, then watched vagal nerve activity change. That tests cause, but only in mice.
How many?	Small groups, which is normal for this kind of lab work: for example, 5 to 9 mice for some nerve recordings and 9 connected cell pairs for the timing measurement.
How long?	Minutes to hours. These were short experiments on nerve signals, not long-term studies of health or behavior.
Who paid for it?	The paper lists NIH grants, the AGA-Elsevier pilot research award, DARPA, The Hartwell Foundation, The Dana Foundation, and The Grass Foundation; one author was supported as a Howard Hughes Medical Institute fellow.
Is something being sold?	No product, but the paper states that some findings were used to file a provisional patent application.

The conclusion: this is strong, careful basic science showing a new kind of gut-to-nerve connection in mice. It does not show that humans have the same synapses working the same way, and it says nothing yet about treating any disease.

Hype Meter: "Your gut cells are wired straight to your brain"

Strong	Moderate	**Preliminary**	Hype

Verdict: Preliminary. In mice, some gut sensor cells (neuropod cells) form synapses with vagal sensory neurons and pass signals within milliseconds, connecting the gut lining to the brainstem through one synapse plus the vagus nerve. These studies are careful, but they are mouse studies in a very new field, and "straight to your brain" skips the vagal neuron in between. **What would change the grade:** Finding the same synapses and fast signaling in human gut tissue, and then showing they matter for how people sense food, would move it to Moderate or higher.

2.11 Feeling Full: CCK, GLP-1, and Satiety Signals

Back to Sam at lunch on the day of his chemistry final. After a few bites, he feels full. What's actually telling his brain to stop eating?

A **satiety signal** is any signal from the gut or body that tells the brain that enough food has been eaten, producing the feeling of fullness and reducing the urge to keep eating. Satiety signals come in two main flavors: nerve signals from stretch (the stomach is physically filling up) and chemical signals from the gut hormones released when nutrients arrive.

Cholecystokinin (CCK) is a gut hormone released by enteroendocrine cells in the small intestine (called I-cells), mainly when protein-rich and fat-rich food arrives, that helps digest food and acts as a satiety signal partly by exciting vagal sensory nerves. CCK was discovered in 1928 as a substance that makes the gallbladder contract, which is where its name comes from. A 2017 review by Jens Rehfeld lists its jobs: squeezing the gallbladder, boosting digestive enzymes from the pancreas, changing gut movement, reducing stomach acid, and producing satiety. In 1973, Gibbs, Young, and Smith reported that injecting CCK reduced how much food rats ate.

Smith and Gibbs later recalled that CCK was simply the first gut hormone their team chose to test, and the first experiments worked. Human studies have since backed up the basic idea: a 2023 review of 15 randomized trials in healthy adults, by Warrilow and colleagues, found that CCK helps bring a meal to an end sooner (satiation), but found no evidence that it causes long-term weight loss. The 2018 Bonaz review describes CCK, GLP-1, and another gut hormone called PYY as reaching the brain through vagal afferents, though much of the evidence for that vagal route comes from animals.

GLP-1 (glucagon-like peptide 1) is a gut hormone released after eating by enteroendocrine cells called L-cells in the intestinal lining, that boosts insulin release when blood sugar is high, slows stomach emptying, and reduces food intake. A 2019 review by Müller and colleagues lists those three effects. GLP-1 has become famous outside biology class, too. The Gribble and Reimann review notes that drugs that copy GLP-1 (GLP-1 mimetics) are licensed medicines, used for type 2 diabetes and for obesity. As of 2026, some of these drugs are FDA approved for obesity in teens 12 and older. For example, semaglutide, sold as Wegovy, gained that

approval in December 2022. Those medicines are prescribed and monitored by doctors; this chapter teaches how the natural hormone works, not who should take them.

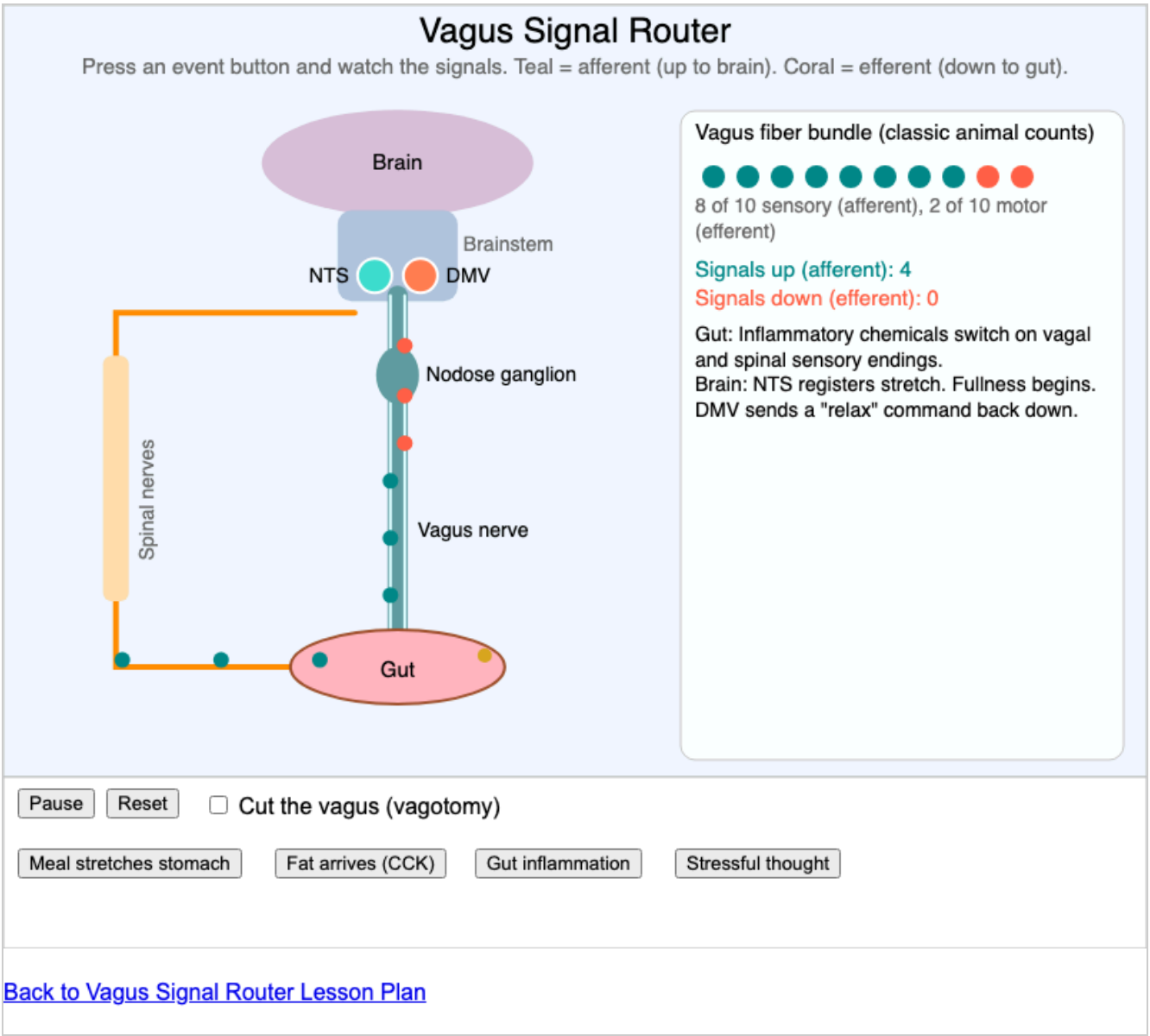
Signal	Where it comes from	What triggers it	Main effects	Route to the brain
Stomach stretch	Stretch-sensing vagal endings in the stomach wall	Food volume	Fullness; triggers gastric accommodation	Vagal afferents to NTS
CCK	Enteroendocrine cells (I-cells) in the small intestine	Protein-rich and fat-rich food	Gallbladder squeezes; fullness; slower stomach emptying	Mainly vagal afferents (mostly animal evidence)
GLP-1	Enteroendocrine cells (L-cells) in the intestinal lining	A meal	More insulin when blood sugar is high; slower stomach emptying; less eating	Vagal afferents and the bloodstream

So what happened to Sam? Stress may change how his stomach and its brainstem circuits behave (the Travagli review notes these circuits shift after stress), and the sympathetic system slows digestion when he's keyed up. His IBS may also make normal stretch feel bigger (Chapter 8 explains how). A test-day sandwich can feel huge when the stomach isn't relaxing to make room.

2.12 Trying It Yourself: The Vagus Signal Router

You now know all the parts: afferent fibers carrying news up, the nodose ganglion, the NTS and DMV in the brainstem, efferent fibers carrying commands down, the spinal route, and gut hormones like CCK. The simulation below puts them together. Teal pulses are afferent signals, and coral pulses are efferent signals.

Diagram: Vagus Signal Router



Back to Vagus Signal Router Lesson Plan

Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch02-vagus-signal-router/main.html

Open the Vagus Signal Router fullscreen

MicroSim specification: Vagus Signal Router

Type: microsim **sim-id:** ch02-vagus-signal-router
Library: p5.js
Status: Implemented
Bloom Level: Analyze
Bloom Verb: compare
Learning Objective: The learner will compare afferent (gut-to-brain) and efferent (brain-to-gut) vagus signaling across four everyday events, and contrast the vagal route with the spinal route.

Canvas: 540 px drawing area plus 120 px controls (iframe 662 px); responsive to about 380 px wide, where the info panel moves below the diagram.

Controls: Start/Pause, Reset, "Cut the vagus (vagotomy)" checkbox, and four event buttons: Meal stretches stomach, Fat arrives (CCK), Gut inflammation, Stressful thought.

Rules: Meal: 4 afferent stretch pulses up the vagus; each arrival at the NTS sends an efferent "relax" pulse down (gastric accommodation). Fat: an enteroendocrine cell flashes "CCK," then 4 afferent pulses rise (satiety signal); some arrivals send an efferent "empty more slowly" pulse. Inflammation: 3 afferent pulses up the vagus and 3 up the spinal route (nausea and unwellness via the vagus; discomfort and pain via spinal nerves); some vagal arrivals send an efferent anti-inflammatory pulse, labeled as studied mostly in animals. Stressful thought: starts in the brain; DMV output dims and 3 sympathetic pulses travel down the spinal route (digestion slows). With the vagus cut, vagal pulses stop at the cut in both directions; spinal pulses still pass.

Feedback: Counters for signals up and signals down; a status panel names what the gut and brain are doing; a fixed fiber bundle shows 8 of 10 fibers sensory (classic animal counts, about 80%).

Provenance: Sections 2.5 to 2.11 (Prescott and Liberles 2022; Bonaz 2018; Travagli and Anselmi 2016; Farré and Tack 2013; Brookes 2013; Brierley 2018). Pulse speeds and counts are illustrative.

Start with **Meal stretches stomach** and watch the order of events: teal pulses rise to the NTS first, and only then do coral pulses leave the DMV and travel down. That's the vago-vagal reflex: information up, a command down. Watch the counters, too. After a few events, notice how many more signals travel up than down, and compare that with the 8-of-10 fiber bundle.

Then try **Gut inflammation** and notice that two routes light up: the vagus and the spinal nerves. Now check **Cut the vagus (vagotomy)** and repeat each event. Predict first: which events still reach the brain? Stretch and CCK signals stop at the cut, and the stomach never gets its "relax" command. But inflammation still sends signals up the spinal route, and a stressful thought still slows digestion through sympathetic nerves. Keep that result in mind for the At the Bedside case.

What this model leaves out

- A real vagus nerve has tens of thousands of fibers in each branch, not ten, and the 8-of-10 split is an approximate figure from animal counts.
- Real signals are streams of electrical impulses of different speeds; gut hormones like GLP-1 also travel through the blood, which the sim doesn't show.
- The brainstem connects to many higher brain areas (hunger, stress, emotion); the sim shows only the NTS and DMV.
- The sim doesn't show the heart, lungs, and other organs the vagus also serves, or the pelvic nerves to the end of the colon.
- Timings are made up for teaching, and real vagotomy effects on symptoms vary from person to person.

2.13 Vagal Tone: Can You Measure Your Vagus Nerve?

Wellness posts love the phrase "vagal tone." Here's what it means.

Vagal tone is the ongoing, background level of activity in the vagus nerve's efferent (motor) fibers, most often estimated through its calming effect on the heart. Even at rest, the vagus gently brakes your heart.

Researchers usually estimate vagal tone indirectly, using **heart rate variability** (HRV), the small, normal changes in time between one heartbeat and the next. A 2017 review by Laborde, Mosley, and Thayer explains that HRV can index cardiac vagal tone, meaning the parasympathetic contribution to controlling the heart. But the same review warns that HRV findings are easy to misinterpret and need careful methods. Breathing rate, posture, caffeine, exercise, time of day, and the exact way the measurement is taken all change HRV.

The 2018 Bonaz review notes that lower vagal tone has been described in some people with IBD and IBS. That's an interesting association, but it doesn't tell us which comes first: low vagal tone could contribute to gut problems, gut problems could lower vagal tone, or a third factor (like stress, poor sleep, or medicines) could affect both.

Your watch measures your heart, not your gut



A smartwatch HRV number is an indirect estimate of my effect on your *heart*, and it shifts with breathing, sleep, caffeine, and how still you sit. It doesn't directly measure my gut fibers, and it can't tell you whether your vagus nerve is "healthy."

Posts promise that splashing cold water on your face, taking an ice bath, humming, singing, or gargling will "reset" or "activate" your vagus nerve. Some of this has a grain of truth. In a 2018 lab study of 61 healthy

adults, Jungmann and colleagues found that briefly cooling the side of the neck slightly raised HRV and lowered heart rate compared with a no-cooling condition; the authors called it a first step toward designing a wearable device. A 2018 systematic review by Zaccaro and colleagues, which included 15 studies of healthy people, found that slow breathing (under 10 breaths a minute) increased HRV and was linked to feeling calmer.

But there's a big leap from "a short change in heart-rate measurements in healthy volunteers" to "cures anxiety" or "heals your gut."

Hype Meter: "Cold plunges, humming, or gargling reset your vagus nerve and cure anxiety"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. Small lab studies in healthy adults show that brief cold on the face or neck, or slow breathing, can briefly shift heart rate and HRV, which are indirect estimates of vagal activity at the heart. None of the studies used in this chapter show that these tricks "reset" the vagus nerve, change gut function, or treat an anxiety disorder. "Reset" has no scientific meaning here. **What would change the grade:** Randomized controlled trials in people with anxiety, comparing a specific practice with a believable placebo practice over weeks, measuring anxiety symptoms (not just HRV), could move a specific technique, such as slow breathing, up to Preliminary or Moderate. Anxiety treatments that already have strong evidence are covered in Chapter 18.

For families

If your teen gets stomachaches or loses their appetite before tests, games, or performances, the feeling is real: stress signals really do change how the stomach moves and how gut signals reach the brain. Saying "it's all in your head" can feel dismissive, even though the brain is involved. Try something like, "Your body is reacting to a big day; what would help right now?" If symptoms happen often, interfere with eating, or come with weight loss, pain that wakes them up, or blood in the stool, that's a reason to see a doctor, not to try a vagus "hack."

2.14 When Surgeons Cut the Vagus: Vagotomy

In the mid-1900s, ulcers (open sores in the lining of the stomach or the first part of the small intestine) often needed surgery. Doctors knew stomach acid played a big part, and that the vagus helps tell the stomach to make acid. So surgeons tried cutting it.

Vagotomy is a surgery that cuts all or part of the vagus nerve to the stomach, historically done to reduce stomach acid in people with ulcers. The American surgeon Lester Dragstedt at the University of Chicago pioneered vagotomy for peptic ulcer disease in the 1940s, according to a 1994 history by Modlin and Darr.

Cutting the main trunks (truncal vagotomy) reduced acid, but it also removed the vagus's efferent control of stomach movement. A clinical overview for doctors on *Patient.info* explains that truncal vagotomy alone could stop the stomach from emptying properly, so surgeons added a second operation to widen the stomach's exit (a pyloroplasty). That overview also notes that diarrhea is common after vagotomy. Surgeons developed more selective versions that cut only the branches to the acid-making part of the stomach, which had fewer side effects but higher rates of ulcers coming back.

Then the reasons for the surgery largely disappeared. Medicines that powerfully reduce stomach acid became available, and doctors discovered that a bacterium, *Helicobacter pylori*, causes many ulcers and can be treated with antibiotics. A 2014 review by Lagoo, Pappas, and Perez concludes that the role of vagotomy in ulcer care is now significantly limited, kept mainly for emergencies and rare hard-to-treat cases.

Doctors still meet older patients who had a vagotomy decades ago, like the patient below. And interest in the vagus has turned in a new direction: instead of cutting it, researchers stimulate it. Implanted vagus nerve stimulators are FDA approved for some people with hard-to-treat epilepsy and depression. In August 2021 the FDA approved one called Vivistim, used during rehabilitation therapy, for people with long-lasting, moderate to severe arm weakness after an ischemic stroke. And in July 2025 the FDA approved one called the SetPoint System for adults with moderate to severe rheumatoid arthritis who hadn't responded well to biologic or targeted drugs. Vagus nerve stimulation is **not** approved for Crohn's disease, IBS, or anxiety.

One related device is worth knowing about, so you don't mix it up: in June 2019 the FDA authorized IB-Stim, a small stimulator worn behind the ear that sends mild pulses to nerves in and around the ear, as an add-on to help reduce IBS-related belly pain in patients 11 to 18 years old. That was a De Novo authorization, the FDA route for new kinds of lower-risk devices. It is a different, lighter review than the full premarket approval that implanted vagus nerve stimulators go through, and it does not mean implanted vagus nerve stimulation is approved for IBS. Chapter 17 covers these devices in detail.

At the Bedside: Full After a Few Bites

Meet the patient (fictional)

Walter is 74 and recently moved to be closer to his daughter. At his first visit with a new gastroenterologist, he explains that he has felt full after just a few bites for most of his adult life, and that he has bouts of loose, urgent stool, especially after larger meals. Lately he has started skipping family dinners at restaurants because he worries about needing a bathroom quickly. His daughter mentions that he "had stomach surgery back in the 1970s."

What the doctor checks: The doctor takes a careful history, including old surgical records. They show that Walter had a truncal vagotomy and pyloroplasty for a duodenal ulcer in 1976. The doctor asks about weight changes, what his meals look like, when symptoms happen, and any warning signs such as blood in the stool, vomiting, or night sweats. Because Walter is older and his symptoms are long-standing, the doctor also

reviews his medicines and orders tests to make sure nothing new (such as an infection or another bowel disease) is adding to the problem.

Connecting the signals: When the main vagal trunks were cut, Walter lost most of the efferent signals from his DMV to his stomach. Normally, a meal stretches the stomach, afferent signals reach the NTS, and efferent signals come back down to relax the upper stomach (gastric accommodation). Without that command, his stomach can't expand as easily, so it feels full quickly. The widened stomach exit from his pyloroplasty also lets food leave faster, and diarrhea is a known, common effect after vagotomy.

Diagnosis: Long-term symptoms after vagotomy (sometimes called post-vagotomy syndrome): early fullness and diarrhea, with tests showing no new disease.

Why it happens: This is the Vagus Signal Router's "cut" setting in real life. Signals up and down the vagus can't cross the cut, so the brainstem can't run its vago-vagal reflexes for the stomach. Walter's enteric nervous system still works (it runs local reflexes, as Chapter 1 showed), and his spinal nerves still carry sensations, so his gut isn't silent, just missing an important line of communication.

The mind-body side: Walter's biggest problem right now isn't the biology; it's that he has started avoiding meals with his family. Worry about urgent bathroom trips can make people feel more on edge during meals, and stress signals can make the gut more reactive, which feeds the worry. The care team takes this seriously: they ask how symptoms affect his life, and they may suggest planning ahead (for example, knowing where restrooms are) and talking with a counselor if the worry keeps growing.

Treatment today: There's no way to reconnect a vagus nerve cut decades ago. Care focuses on symptoms. A dietitian can help Walter find a meal pattern that works for him, and his doctor may consider medicines that reduce diarrhea, depending on the cause and his other health conditions. Each plan is individual and is worked out with his care team.

What's new in research: Researchers are now testing whether *stimulating* the vagus could calm gut inflammation. In a 2016 pilot study, Bonaz and colleagues implanted vagus nerve stimulators in 7 adults with active Crohn's disease and followed them for 6 months. Five improved, with lower inflammation markers, while two were removed from the study at 3 months because they got worse. There was no comparison group. A 2023 proof-of-concept study by Sahn and colleagues tried a noninvasive stimulator clipped to the ear in 22 young people aged 10 to 21 with mild to moderate IBD for 16 weeks; a stool marker of gut inflammation fell by at least half in 11 of the 17 participants who started with high levels. In the first 4 weeks, each participant got 2 weeks of real stimulation and 2 weeks of a sham (fake) version; after that, everyone got real stimulation, so most of the study had no control group. **Evidence grade: Preliminary.** Vagus nerve stimulation is not approved for Crohn's disease.

Your turn: reason through a variation

Suppose Walter had instead had a highly selective vagotomy, which cuts only the vagal branches to the acid-making part of the stomach and leaves the branches to the stomach's lower part and the intestines. Would you expect his symptoms to be the same, milder, or worse? What trade-off did surgeons accept with this version?

Answer: Milder. Because more efferent control of stomach emptying is kept, the stomach can still empty in a more controlled way without a pyloroplasty, so diarrhea is less of a problem. The trade-off is that cutting fewer fibers reduces acid less completely, so ulcers came back more often after highly selective vagotomy.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: The vagus nerve mostly sends commands from the brain down to the gut.
Reality: Most vagus fibers are sensory. Classic fiber counts in animals put about 80% of them as afferent, carrying information from the body up to the brainstem.

Myth: The vagus nerve is just a "calm down" switch.
Reality: The vagus carries a huge range of information (stretch, nutrients, hormones, inflammation) and helps run reflexes such as gastric accommodation. Its parasympathetic effects matter, but it is mainly a sensory cable, not a relaxation button.

Myth: Your smartwatch measures your vagal tone directly.
Reality: HRV is an indirect estimate of the vagus nerve's effect on the heart, and it changes with breathing, posture, caffeine, sleep, and how it's measured. It doesn't measure the vagus fibers to the gut.

Myth: The vagus is the only way the gut talks to the brain.
Reality: Spinal afferent nerves carry many gut sensations, including much of gut pain, and gut hormones and immune signals travel through the blood. The vagus is one important route among several.

Myth: Neuropod cells prove your gut is wired directly into your brain.
Reality: Neuropod cells were described in mice, where they connect to vagal sensory neurons, which then signal the brainstem. Whether human gut cells work the same way is still being studied.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Hum for 5 minutes a day to activate your vagus nerve and heal your gut. Your gut-brain connection will thank you!"

Grade: Hype. Slow breathing can raise heart rate variability in healthy people, and humming may slow breathing, but HRV is an indirect estimate of the vagus nerve's effect on the heart, not the gut. None of the evidence in this chapter shows that humming changes gut function or heals any gut condition, and "activate" is vague. A careful version would say: "Slow breathing can briefly change heart-rate measures linked to the vagus nerve, and some people find it calming; it hasn't been shown to treat gut disease."

2. Predict: Sam is nervous before a race and eats a big bowl of pasta an hour before the start. Predict how his stomach might respond, using the parasympathetic and sympathetic branches.

Race nerves boost sympathetic (fight-or-flight) activity and dampen vagal output, so his stomach may relax and empty less smoothly, and digestion slows. The pasta stretches his stomach, and stretch signals still travel up the vagus, so he may feel uncomfortably full or queasy. The likely result is a heavy, unsettled stomach at the start line. This is a reason many athletes experiment with timing meals, ideally with advice from a coach or doctor.

3. Explain: Riya feels nauseated during Crohn's flares even when she hasn't eaten anything new. Explain the pathway from her inflamed intestine to the feeling of nausea.

Inflammation releases chemicals that can switch on sensory nerve endings in the gut wall. Afferent signals travel up the vagus nerve, past the nodose ganglion, to the NTS in the brainstem, which sits among the circuits that produce nausea; spinal afferents also carry discomfort signals. The brain turns this incoming information into the conscious feeling of nausea, which is an example of interoception. The feeling is real information from her gut, not something imagined.

4. Apply: In an experiment, rats are given an injection of CCK just before a meal. A second group gets the same injection after their vagus nerves have been cut. Predict the results.

The first group should eat less, because CCK is a satiety signal (Gibbs and colleagues showed this in rats in 1973). In the second group, the effect should be much weaker, because CCK works largely by exciting vagal sensory nerves, and the cut prevents those signals from reaching the NTS. If the vagotomized rats still ate a little less, that would suggest CCK also acts through other routes.

5. Read the data. Here are two estimates of how vagus nerve fibers split between sensory (afferent) and motor (efferent). The first is the classic figure as cited by Prescott and Liberles (2022); the second is from a careful rat study (Prechtl and Powley, 1990).

Source	Animal and nerve region	Finding
Classic animal fiber counts: Foley and DuBois, 1937 (as cited by Prescott and Liberles, 2022)	Cat vagus nerve	About 80% of fibers sensory
Prechtl and Powley, 1990	Rat abdominal vagus (6 animals examined in detail)	Motor fibers may be over a quarter of all fibers; 22,272 fibers counted in the main trunks, 26,930 summed across five branches

5. What does this data show, and what can't it show?

Both sources agree that most vagus fibers are sensory, but they disagree on how many: if motor fibers are over 25%, sensory fibers are under 75%, not 80%. The branch total being about 21% higher than the trunk total shows that counting depends on where and how you count (the authors think extra fibers joined from outside the vagus). The data can't tell us the exact human figure, because both come from animals and the 1937 count is old and not easy to check. A useful follow-up would be a modern fiber count of human vagus nerves at several levels, using the same method for every branch.

Exercises

Remember

1. What is the difference between an afferent signal and an efferent signal?

Answer

An afferent signal travels toward the central nervous system (usually sensory information), and an efferent signal travels away from it to muscles, glands, or organs (usually a command).

1. Name the two brainstem nuclei of the vagus nerve covered in this chapter and say what each does.

Answer

The nucleus tractus solitarius (NTS) receives incoming sensory signals from the vagus. The dorsal motor nucleus (DMV) sends efferent signals down the vagus to the stomach and intestines.

Understand

1. Explain why the statement "the vagus nerve is the brain's control cable for the gut" is misleading.

Answer

Most vagus fibers (about 80% by classic animal counts) are sensory and carry information up to the brain, so the nerve is mainly a listening line. Its efferent fibers also work through the enteric nervous system rather than controlling gut muscle directly.

1. Explain why a smartwatch's HRV number is an indirect measure of vagal tone.

Answer

HRV reflects the vagus nerve's braking effect on the heart, mixed with many other influences such as breathing, posture, caffeine, and sleep. It doesn't record vagus nerve activity directly, and it says nothing direct about the vagus fibers to the gut.

Apply

1. Use the Vagus Signal Router. Trigger each of the four events three times with the vagus intact, and record the "Signals up" and "Signals down" counters. Then reset, cut the vagus, and repeat. Make a table of your results and describe which events still reach the brain after vagotomy, and by which route.
2. A friend says, "Gut hormones are just like nerve signals." Using CCK and GLP-1 as examples, describe one way gut hormones are like nerve signals and one way they are different.

Analyze

1. Compare the 2016 Williams mouse study (different vagal neurons sense stretch and nutrients) with the 2016 Bonaz pilot study of vagus nerve stimulation in 7 people with Crohn's disease. For each, answer three of the six questions (mouse or human, correlation or cause, how many). Which study tells you more about humans, and which is better at showing cause?
2. Sam feels sick before races and full early on test days. List at least three different pathways from this chapter (nerves, brainstem circuits, hormones, autonomic branches) that could contribute, and explain how you might design an observation or experiment to tell them apart.

Evaluate

1. A company sells a $200 earbud device that it says "stimulates your vagus nerve to fix your digestion." Using the evidence in this chapter, including what is and isn't FDA approved, judge this claim. What evidence would you need to see before you believed it?
2. Some writers say the "80%" figure should be dropped from textbooks because it comes from old animal counts. Others say it's still a useful approximation. Write a one-paragraph argument for which side you agree with, using the Prechtl and Powley data.

Create

1. Design an experiment, using mice, that would test whether neuropod cells are needed for the feeling of fullness after a sugary meal. Describe your groups, what you would change, what you would measure, and the result that would support your hypothesis.
2. Create a one-page infographic or comic strip that follows a single bite of food from the moment it stretches the stomach to the moment the stomach relaxes, labeling every afferent and efferent step and naming the nodose ganglion, NTS, and DMV.

Key Takeaways

- The vagus nerve (cranial nerve X) is the longest cranial nerve and the main parasympathetic nerve to the gut. It carries both afferent (gut-to-brain) and efferent (brain-to-gut) fibers.
- Most vagus fibers are sensory. Classic fiber counts in animals put the figure at about 80%, though careful counts show the exact share varies.
- Sensory signals pass through the nodose ganglion to the nucleus tractus solitarius in the brainstem; the dorsal motor nucleus next door sends commands back down, creating vago-vagal reflexes such as gastric accommodation.
- The vagus isn't the only route: spinal afferent nerves carry many gut sensations, including much of gut pain, and gut hormones also travel through the blood.
- Enteroendocrine cells sense nutrients and release gut hormones such as CCK and GLP-1, which act as satiety signals; in mice, some of these cells (neuropod cells) form fast synapses with vagal neurons.
- Vagal tone is usually estimated indirectly through heart rate variability. Claims that cold plunges, humming, or gargling "reset" the vagus nerve and cure anxiety are Hype.
- Vagotomy, once a common ulcer surgery, shows what the vagus does for the stomach: without it, accommodation and controlled emptying suffer.

You rode the whole highway!



You can now trace a signal from the gut wall to the brainstem and back, and you know why most of my traffic heads uphill. Next, in Chapter 3, we'll meet the trillions of microbes living in your gut and find out what they might add to the conversation.

Quiz: The Vagus Highway

Test your understanding of Chapter 2. Choose the best answer, then click **Show Answer** to check.

Question 1

Which statement best describes an afferent signal?

A. A command sent from the brain to make gut muscle contract

B. A signal carried toward the central nervous system, usually sensory information

C. A hormone released into the blood by the stomach

D. A signal that travels only between neurons inside the gut wall

Show Answer

The correct answer is **B**. Afferent signals travel toward the brain or spinal cord ("afferent arrives") and usually carry sensory information. Option A describes an efferent signal, an easy mix-up.

Concept Tested: Afferent Signal **Bloom's Level:** Remember

Question 2

Where do the sensory signals carried by the vagus nerve first arrive in the brain?

A. The dorsal motor nucleus

B. The nodose ganglion

C. The cerebral cortex

D. The nucleus tractus solitarius in the brainstem

Show Answer

The correct answer is **D**. Vagal sensory fibers end mainly in the nucleus tractus solitarius (NTS) in the medulla. The nodose ganglion (B) holds their cell bodies, but it sits in the neck outside the brain, and the dorsal motor nucleus (A) sends signals out, not in.

Concept Tested: Nucleus Tractus Solitarius **Bloom's Level:** Remember

Question 3

Which cell type is a rare, hormone-releasing sensor scattered among the cells lining the intestine?

A. Enteroendocrine cell

B. Enteric glial cell

C. Interstitial cell of Cajal

D. Nodose neuron

Show Answer

The correct answer is **A**. Enteroendocrine cells make up about 1% of intestinal lining cells and release gut hormones such as CCK and GLP-1. Interstitial cells of Cajal (C) are pacemaker cells in the muscle layer, not hormone-releasing sensors.

Concept Tested: Enteroendocrine Cell **Bloom's Level:** Remember

Question 4

Why does this book say "Most vagus nerve fibers carry signals from the body to the brain. Classic fiber counts in animals put the figure at about 80%" instead of simply "80% of vagus fibers are sensory"?

A. Because the true figure in humans is known to be exactly 90%

B. Because the vagus nerve has no motor fibers at all

C. Because the 80% figure comes from old animal counts, and careful studies show the exact share varies

D. Because sensory fibers can't be counted under a microscope

Show Answer

The correct answer is **C**. The 80% figure traces back to fiber counts in cats, and a careful 1990 rat study found that motor fibers in the abdominal vagus may be over a quarter of the total. The majority-sensory point is solid; the exact number is approximate. Option A is wrong because no modern human count settles the figure.

Concept Tested: Vagus Nerve **Bloom's Level:** Understand

Question 5

How does a vago-vagal reflex help the stomach handle a meal?

A. The ENS sends a signal to the spinal cord, which tells the stomach to empty faster.

B. Stretch signals travel up the vagus to the NTS, and the DMV sends a command back down that relaxes the upper stomach.

C. The brain's cortex decides consciously to relax the stomach after every bite.

D. Gut hormones travel to the heart, which slows down to make room for food.

Show Answer

The correct answer is **B**. In gastric accommodation, afferent stretch signals reach the NTS, and efferent signals from the dorsal motor nucleus travel down the vagus to relax the upper stomach. Option C is wrong because this reflex runs in the brainstem without conscious decisions.

Concept Tested: Dorsal Motor Nucleus **Bloom's Level:** Understand

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Question 6

Which statement about heart rate variability (HRV) matches the evidence in this chapter?

A. HRV directly records electrical activity in the vagus fibers to the gut.

B. HRV is unaffected by breathing, posture, or caffeine.

C. A high HRV proves that someone's gut is healthy.

D. HRV is an indirect estimate of vagal tone at the heart and is easy to misinterpret.

Show Answer

The correct answer is **D**. Researchers use HRV to index cardiac vagal tone, but it changes with breathing, posture, caffeine, and measurement methods, and it says nothing direct about the vagus fibers to the gut. Option A is the common smartwatch misconception.

Concept Tested: Vagal Tone **Bloom's Level:** Understand

Question 7

A 70-year-old had his main vagal trunks cut decades ago to treat an ulcer. He now feels full after a few bites. Which explanation fits best?

A. Without efferent vagal signals, his upper stomach can't relax as well to make room for food.

B. His enteric nervous system was removed during the surgery.

C. His spinal nerves can no longer carry any gut sensations.

D. Cutting the vagus made his stomach produce much more acid.

Show Answer

The correct answer is **A**. Vagotomy removes the efferent part of the vago-vagal reflex that relaxes the upper stomach during a meal, so it fills up quickly. Option B is wrong because the ENS stays in the gut wall and keeps running local reflexes, and option D is backwards: vagotomy was done to reduce acid.

Concept Tested: Vagotomy **Bloom's Level:** Apply

Question 8

Riya has strong lower-belly pain and urgency during a Crohn's flare. A classmate says, "That pain must travel only through the vagus nerve." What is the best response?

A. That's right, because the vagus is the only nerve connecting the gut to the brain.

B. That's right, because pain signals can't travel through the spinal cord.

C. Not quite: spinal afferent nerves carry many gut sensations, including much of gut pain, especially from the colon and rectum.

D. Not quite: gut pain is created entirely inside the gut and never reaches the brain.

Show Answer

The correct answer is **C**. Gut sensory signals travel by three pathways, one vagal and two spinal, and spinal afferents to the colon and rectum give rise to discomfort, urgency, and pain. Option A is the misconception that the vagus is the only gut-brain route.

Concept Tested: Spinal Afferent Nerve **Bloom's Level:** Apply

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Question 9

In 2018, researchers showed that some gut sensor cells form synapses with vagal neurons and signal within milliseconds. Which is the most accurate way to describe this evidence?

A. Strong evidence that human gut cells are wired directly to the brain

B. Careful experiments in mice that test cause, but that have not yet been confirmed in humans

C. A correlation study in people that can't show cause

D. A marketing claim with no lab experiments behind it

Show Answer

The correct answer is **B**. The neuropod cell study switched gut cells on and off and blocked glutamate in mice, which tests cause, but it was done in mice and found a connection to vagal neurons, not straight to the brain. That's why the Hype Meter grade is Preliminary. Option A overstates both the species and the wiring.

Concept Tested: Neuropod Cell **Bloom's Level:** Analyze

Question 10

Rats given CCK before a meal eat less. Suppose an experiment finds that in rats whose vagus nerves were cut, CCK has a much smaller effect. What would this comparison suggest?

A. CCK has no effect on eating at all.

B. CCK works only by traveling to the brain through the blood.

C. Cutting the vagus makes rats hungrier for every food.

D. CCK's satiety effect depends largely on vagal afferent signals.

Show Answer

The correct answer is **D**. If removing the vagal route weakens the effect, that suggests the vagus carries much of CCK's satiety signal to the brainstem. Option B is the opposite conclusion; if CCK worked only through the blood, cutting the vagus wouldn't matter much.

Concept Tested: Cholecystokinin **Bloom's Level:** Analyze

Chapter 3: Meet the Microbiome

Summary

Your colon is home to tens of trillions of bacteria, roughly as many bacterial cells as human cells in your whole body. This chapter introduces the gut microbiota and microbiome: who lives there, how a newborn's community forms (and how birth and feeding shape it), how a healthy community keeps harmful bacteria from taking over, and what happens when antibiotics knock it down. You will also learn how scientists read a microbiome using DNA sequencing, why germ-free mice are both powerful and misleading, and why no one has yet defined a single "healthy microbiome." These tools, especially telling correlation from causation, will come back in almost every chapter that follows.

Concepts Covered

1. Microorganism
2. Gut Microbiota
3. Microbiome
4. Bacterial Strain
5. Commensal Bacteria
6. Pathogen
7. Microbial Diversity
8. Dysbiosis
9. Bacteria-to-Human Cell Ratio
10. Microbiome Development
11. Birth Mode and Microbes
12. Human Milk Oligosaccharides
13. Colonization Resistance
14. Antibiotic Disruption
15. 16S rRNA Sequencing
16. Metagenomic Sequencing
17. Animal Model
18. Germ-Free Mouse

19. Correlation vs Causation
20. Defining a Healthy Microbiome

Prerequisites

- Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading), especially the digestive tract, the gut-brain axis, and the Hype Meter.
- Chapter 2: The Vagus Highway, for how signals travel between the gut and the brain.

Let's meet the neighbors



My nerve endings live right next to trillions of microbes, so I'm curious about them too. Microbes are behind some of the most exciting gut-brain research, and also some of the biggest hype online. This chapter gives you the vocabulary and the evidence skills to tell which is which.

3.1 Riya's Antibiotics and a Number That Turned Out to Be Wrong

Riya had a stubborn skin infection on her leg last spring, and her doctor prescribed a course of antibiotics. At her next visit with Dr. Alvarez, her pediatric gastroenterologist, Riya mentioned that her stomach had been a little off during those ten days. Dr. Alvarez nodded. "Antibiotics kill the bacteria causing an infection," she said, "but they also hit the helpful bacteria living in your gut, your microbiome. Most of the time it bounces back. Let's keep an eye on it, since you have Crohn's." (Riya is a fictional 16-year-old with Crohn's disease who appears throughout this book.)

That night, Riya searched "microbiome" and found the same fact on page after page: your body contains ten bacterial cells for every human cell, so you are "only 10% human." It sounds impressive. It's also wrong. In 2016, three scientists at the Weizmann Institute of Science in Israel, Ron Sender, Shai Fuchs, and Ron Milo, carefully redid the math and found that the ratio is much closer to one to one. A number repeated for decades, on websites, in textbooks, and in talks, didn't hold up when someone checked it.

Meanwhile, Riya's friend Sam had his own microbiome encounter. His older cousin posted a video unboxing a home "gut test kit" that promised to reveal "what your microbes say about your mood." Sam rolled his eyes, but he was curious. Can a stool sample really tell you that? We'll come back to that question in Section 3.10.

3.2 A Rainforest in Your Colon

Picture a rainforest. Thousands of kinds of plants, insects, birds, and fungi live together. Some compete for sunlight, some eat each other's leftovers, and some depend on each other completely. No single species is

"the rainforest," and two rainforests on different continents can look very different but both be healthy. A storm or a fire can knock the forest back, and it can regrow, though sometimes not exactly the same way.

Your gut, especially your colon, is a crowded ecosystem like that, made of living things too small to see.

A **microorganism** (or microbe) is a living thing too small to see without a microscope, such as a bacterium, an archaeon, a single-celled fungus like yeast, or a single-celled parasite. Viruses are often grouped with microbes too, although they are not cells. Most microorganisms are harmless to people, and many are essential.

Scientists use two related words that people often mix up. A 2020 expert panel led by Gabriele Berg proposed clear definitions and recommended keeping the two terms separate:

- The **gut microbiota** is the community of living microorganisms that live in the digestive tract: the bacteria, archaea, fungi, and other microbes themselves.
- The **microbiome** is the microbiota plus its "theater of activity": the microbes' genes, the molecules they make, and the environment they live in. In everyday talk, people often say "microbiome" when they mean just the microbes, and this book sometimes does too when the difference doesn't matter.

Here is a quick way to keep them straight: the microbiota is the cast of characters, and the microbiome is the whole play, including the script (their genes) and what they do on stage (the molecules they make).

Almost all gut bacteria live in the colon (large intestine), where food moves slowly and there is little oxygen. The stomach is too acidic for most bacteria, and the small intestine moves contents through too quickly for huge populations to build up. Many colon bacteria are anaerobes, meaning they grow without oxygen, and many have picky needs, which is one reason they can be hard to grow in a lab.

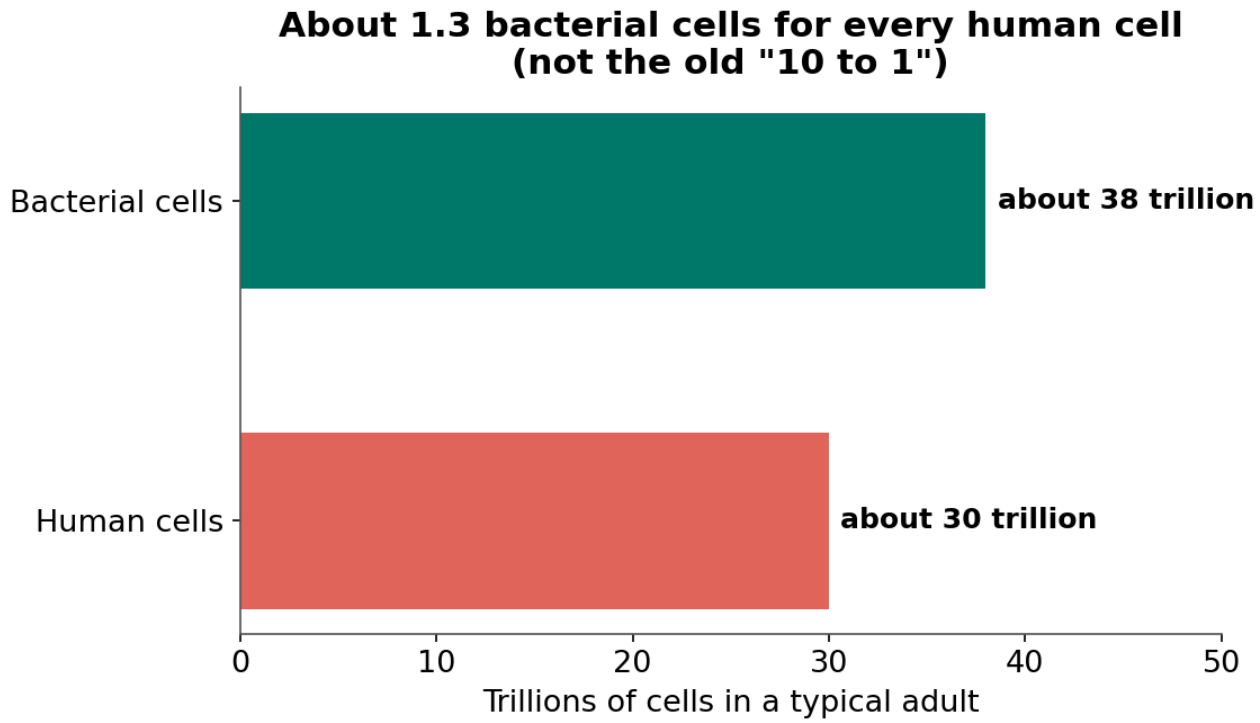
3.3 How Many Microbes? The Bacteria-to-Human Cell Ratio

The **bacteria-to-human cell ratio** is the number of bacterial cells in a person's body divided by the number of human cells. Here is the careful version of the fact, used throughout this book:

> A typical adult has roughly 38 trillion bacterial cells and 30 trillion human cells, about 1.3 to 1. The old "10 to 1" figure is wrong.

Sender, Fuchs, and Milo published their full estimate in 2016 in the journal *PLoS Biology*, using a "reference man," a standard 70-kilogram adult used in calculations. They estimated about 38 trillion bacteria (written 3.8×10^{13}) and about 30 trillion human cells (3.0×10^{13}). They also found that all those bacteria weigh only about 0.2 kilograms in total, because bacterial cells are tiny.

$$\frac{38 \text{ trillion bacteria}}{30 \text{ trillion human cells}} \approx 1.3$$



Source: Sender, Fuchs, and Milo 2016, PLOS Biology. Estimates for a reference adult (20 to 30 years old, about 70 kg); the old "10 to 1" figure is wrong.

Several details make this number more interesting than a single ratio:

- **Most of the bacteria are in the colon.** The colon holds nearly all of them; other body sites add comparatively few.
- **Most of your human cells are blood cells.** About 90% of human cells by count belong to the blood-forming lineage, mostly red blood cells, which are small and extremely numerous.
- **The ratio moves.** The authors estimate an uncertainty of about 25%, and the number varies from person to person. Even a single bowel movement removes a quarter to a third of the bacteria in the colon, which noticeably shifts the ratio for a while.
- **It counts bacteria only.** The microbiome also includes archaea, fungi, and viruses, which aren't in the 1.3 figure.

So you are not "90% bacteria." You are a roughly even partnership. That's still a huge number: tens of trillions of living cells that aren't you, mostly packed into one organ.

Even famous numbers need checking



The "10 to 1" figure was repeated for decades because it sounded cool, not because anyone kept re-checking it. When you see a striking number, ask, "Who measured this, and how?" Even a US government project page still showed the old figure when this book's editors checked it in 2026.

The archived NIH Human Microbiome Project web page still said in October 2026 that microbial cells outnumber human cells "by about ten to one." The project itself did good science, but its page shows how long an outdated number can live online.

3.4 Who Lives There? Strains, Commensals, and Pathogens

Gut bacteria are classified like other living things, from big groups down to small ones. In adults, two large groups (phyla) usually dominate: Bacteroidetes and Firmicutes, with smaller amounts of others, according to the 2018 Bonaz review. (Scientists recently renamed these groups Bacteroidota and Bacillota. This book uses the older names because most of the research it describes uses them.)

Below the level of species, there's an important finer level. A **bacterial strain** is a genetic variant within a single bacterial species: strains of the same species share most of their genes but differ in some, which can change what they do. The classic example is *Escherichia coli* (*E. coli*). The US Centers for Disease Control and Prevention (CDC) explains that most *E. coli* are harmless and are part of a healthy intestinal tract, but some kinds can make people sick with diarrhea, urinary tract infections, pneumonia, and other illnesses. Same species name, very different behavior. That's why researchers and careful product labels name the strain, not just the species.

Most of your gut bacteria are neighbors you get along with. **Commensal bacteria** are bacteria that normally live on or in the body without causing harm, and often provide benefits, such as helping digest fiber or crowding out harmful microbes. A **pathogen** is a microorganism that can cause disease. Some pathogens cause disease in almost anyone they infect. Others, often called opportunists, live quietly in small numbers and cause trouble mainly when the normal community is disturbed or the body's defenses are down.

Term	What it means	Example from this chapter
Commensal bacteria	Normal residents that usually cause no harm and often help	Most *E. coli* strains; fiber-fermenting Bacteroides
Pathogen	A microbe that can cause disease	Disease-causing *E. coli* strains
Opportunist	Usually harmless in small numbers; can cause disease when the community is disrupted	*C. difficile* after antibiotics (Section 3.8)

The line between these categories isn't always fixed. The same species can be a quiet resident in one person and a problem in another, depending on the strain, its numbers, and what else is living nearby.

3.5 Microbial Diversity: Many Kinds, Mixed Evenly

Two forests can have the same number of trees but very different variety: one might be 99% pine, the other a mix of fifty kinds of trees. Ecologists care about both how many kinds there are and how evenly they're mixed.

Microbial diversity is a measure of how many different kinds of microbes live in a community (richness) and how evenly their numbers are spread out (evenness). One common measure is the Shannon diversity index, which goes up when there are more kinds of microbes and when no single kind dominates:

$$H = -\sum_{i} p_i \ln p_i$$

Here p_i is the fraction of the community made up of species i. You don't need to calculate it by hand. Just remember that a community split evenly among many species has a high H, and a community dominated by one species has a low H.

The Human Microbiome Project, funded by the NIH Common Fund from 2007 to 2016, mapped the microbes of healthy volunteers. Its 2012 summary paper in *Nature* described the wide range of community types found in healthy people. A 2012 review by Lozupone and colleagues adds that the gut microbiota is immensely diverse, varies between individuals, and can fluctuate over time, especially during disease and early development.

That individuality matters. In a 2011 study, Dethlefsen and Relman followed the gut bacteria of three adults over 10 months and found that differences between people were the biggest source of variation in their samples. Each person's community wobbled from day to day but stayed close to its own stable average for months.

Is more diversity always better? Often, in adults, lower diversity shows up alongside certain diseases. But "more is better" is too simple, as you'll see in the next section: healthy breastfed babies normally have *low* diversity.

3.6 Microbiome Development: The First Year of Life

Microbiome development is the process by which a newborn's gut, which starts with very few microbes, is colonized and changes over the first years of life toward a more stable, adult-like community. It's a bit like a newly cleared field: the first plants to arrive are fast-growing pioneers, and over time the community becomes richer and more stable.

Birth mode

The first microbes a baby meets depend partly on how the baby is born. **Birth mode and microbes** refers to the way a baby's delivery (vaginal birth or cesarean section, also called C-section) shapes which microbes first colonize the newborn.

The first study to show this clearly was small. In 2010, Dominguez-Bello and colleagues sampled 10 newborns. Babies born vaginally first carried microbes that resembled their mother's vaginal microbes, while babies born by C-section first carried microbes like those found on skin. Because only 10 babies were studied, this was a starting point, not the final word.

Much larger studies followed. In 2019, Shao and colleagues analyzed 1,679 stool samples from 596 full-term babies born in UK hospitals and found that in the first weeks of life, C-section babies showed disrupted transfer of their mothers' *Bacteroides* strains and more colonization by hospital-associated bacteria. In the TEDDY study of 903 children in the US and Europe, published in 2018 by Stewart and colleagues, birth-mode differences were present early but became less important over time, and breastfeeding had a bigger effect on how the microbiome matured.

A 2015 Swedish study by Bäckhed and colleagues also found that C-section babies' microbes resembled their mothers' less in early life.

Breastfeeding and human milk oligosaccharides

Human milk contains something surprising: sugars the baby can't digest. **Human milk oligosaccharides** (HMOs) are a family of complex sugar molecules found in large amounts in human milk that the baby can't digest, which instead feed certain beneficial gut bacteria, such as *Bifidobacterium*. A 2012 review by Lars Bode explains that HMOs were first discovered as a "bifidus factor," food for helpful bacteria. HMOs may also act as decoys that keep some pathogens from sticking to the gut lining. Bode is careful to note that most of that evidence comes from lab, animal, or association studies, and that randomized trials are needed to confirm the benefits in babies.

So breast milk feeds the baby and also feeds selected microbes. That's why exclusively breastfed babies tend to have a gut community dominated by a few milk-loving groups. A 2018 meta-analysis by Ho and colleagues, combining data from 684 infants in several countries, found that exclusively breastfed infants had *lower* diversity in their first 6 months than other infants. That's normal. Bäckhed's study also found that what most pushed the infant microbiome toward an adult-like state was stopping breastfeeding, more than starting solid food.

Hype Meter: "C-section babies start life with different gut microbes"

Strong	Moderate	Preliminary	Hype

Verdict: Strong (for early differences). Large human studies, including a UK study of 596 newborns and the 903-child TEDDY study, confirm that birth mode changes which microbes colonize a baby in the first weeks and months. These differences shrink over the first year or so, and breastfeeding has a larger effect on maturation. Claims that C-section birth causes lifelong disease *through* the microbiome are a different matter: the studies in this chapter don't show that, so any long-term health claim is Preliminary at best. **What would change the grade:** Long-term studies that follow children for years and test whether early microbe differences actually cause later health differences, while accounting for the reasons a C-section was needed, would tell us whether the long-term claims hold up.

For families

Many parents feel guilty after a C-section or when breastfeeding doesn't work out, especially after reading microbiome headlines. The evidence shows early differences in babies' microbes, but those differences fade over the first year, and the research doesn't show that birth mode or formula feeding "ruins" a child's microbiome. Babies are born by C-section and fed formula for good medical and personal reasons. If you have questions about your own child, a pediatrician is the right person to ask, not a test kit or a headline.

3.7 Colonization Resistance: A Full Parking Lot

Imagine a parking lot so full that a newcomer can't find a space. A healthy gut community works a bit like that. When the space and food are already taken by residents, an invader has a hard time settling in.

Colonization resistance is the ability of the normal gut microbiota to prevent harmful microbes from settling in and multiplying, by competing for space and nutrients, making substances that block invaders, and stimulating the body's defenses. A 2013 review by Buffie and Pamer describes how commensal bacteria in mice and humans help protect against infections, including dangerous bacteria that resist many antibiotics, such as *Clostridioides difficile* (*C. difficile*), and how certain groups of commensal bacteria can restore protection after antibiotics in animal experiments.

Colonization resistance is one of the clearest examples of the microbiota helping us. It explains why a disturbed community can open the door to infection, which brings us to antibiotics.

3.8 Antibiotic Disruption

Antibiotics are among the most important medicines ever developed; they save lives by killing the bacteria that cause infections. But most antibiotics can't tell the bacteria causing an infection from the bacteria living peacefully in your colon. **Antibiotic disruption** is the change in the gut microbiota caused by antibiotics: a loss of bacterial numbers and diversity, shifts in which groups dominate, and a recovery afterward that is often fast but not always complete.

How big is the effect, and how complete is recovery? Two human studies give a picture.

In the 2011 Dethlefsen and Relman study, three adults each took two short courses of the antibiotic ciprofloxacin over 10 months. Within 3 to 4 days of starting the drug, each person's gut community lost diversity and shifted in makeup. About a week after each course ended, the communities began returning toward their starting state, but the return was often incomplete. By the end of the study, every person's community had stabilized, but in a state somewhat different from where it began. The responses also differed between people and even between the two courses in the same person.

In 2018, a Danish-led team (first author Albert Palleja) gave 12 healthy young men a 4-day course of three powerful "last-resort" antibiotics at once, then followed their gut bacteria for 6 months using metagenomic sequencing (Section 3.10). Right after the antibiotics, some opportunist bacteria bloomed, while *Bifidobacterium* species and butyrate-producing bacteria dropped. The communities recovered to near their starting makeup within about 1.5 months. But 9 common species that every man carried before treatment were still undetectable in most of the men after 180 days.

Let's apply the six questions from Chapter 1, Section 1.13 to this study.

How to read a gut-brain claim: the 2018 antibiotic recovery study

Question	This study
Mouse or human?	Human: 12 healthy young men in Denmark. No women, children, older adults, or people with illnesses.
Correlation or cause?	Cause, within each person. The researchers gave the antibiotics on purpose and compared each man's microbes before and after. There was no untreated comparison group, but the sudden changes right after the antibiotics make the drugs the very likely cause.
How many?	12 people, with stool samples at several time points. Small, but deeply analyzed with metagenomic sequencing.
How long?	6 months of follow-up after a 4-day course. That's long for this kind of study, but it can't say what happens over years.
Who paid for it?	Mainly the Novo Nordisk Foundation Center for Basic Metabolic Research (an independent center at the University of Copenhagen partly funded by the Novo Nordisk Foundation), plus Danish research councils and diabetes groups. The authors declared no competing interests.
Is something being sold?	No. The antibiotics used are hospital drugs, and no product was promoted.

The conclusion: in healthy young men, the gut community was resilient to a short, very strong antibiotic course, but recovery was not perfect, and a few species seemed to be lost for months. These were unusual "last-resort" antibiotics given together, so the results may not match a typical course of one antibiotic for an ear or sinus infection. And the study didn't measure whether the lost species mattered for health.

Antibiotics can also open the door to a dangerous opportunist. According to the CDC, *C. difficile* is a bacterium that causes diarrhea and inflammation of the colon and is estimated to cause almost half a million infections in the United States each year. People are up to 10 times more likely to get it while taking an antibiotic and during the month after finishing one. This is colonization resistance in reverse: when the normal residents are knocked down, *C. difficile* can take over.

Hype Meter: "One round of antibiotics ruins your microbiome forever"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype (as stated). Human studies show that antibiotics quickly reduce gut diversity, and that recovery can be incomplete, with a few species missing for months in some people. But the same studies show that most of the community regrows within weeks to a couple of months in healthy adults. "Ruins forever" turns a real, modest, long-lasting change into a scare, and it can push people to avoid antibiotics they need. **What would change the grade:** A careful version, "antibiotics can leave small, lasting changes in the gut microbiota," is well supported (Moderate to Strong). Long-term studies showing that those lasting changes harm health would strengthen the case for caution, which doctors already practice by prescribing antibiotics only when needed.

Don't skip antibiotics you need

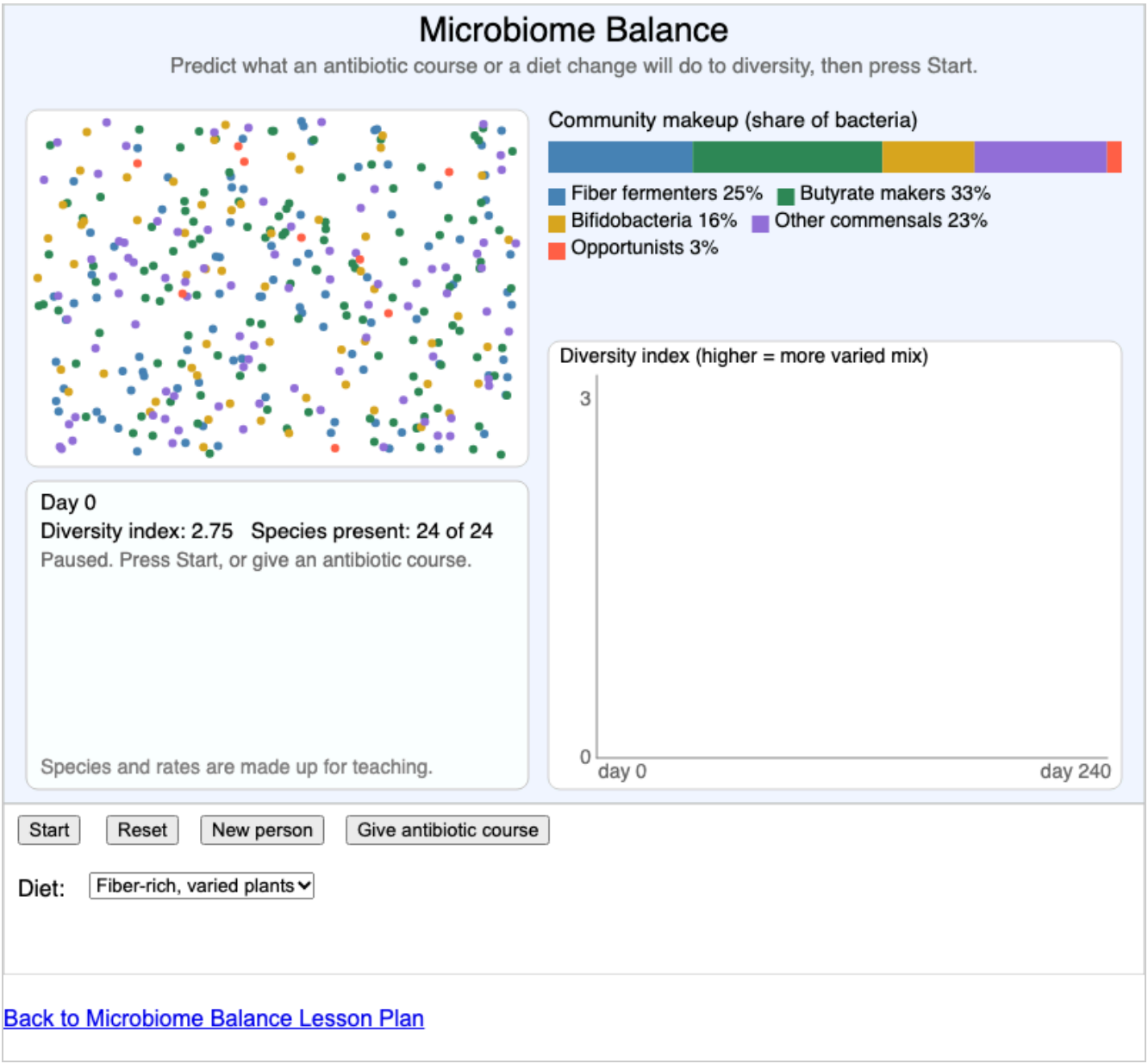


Microbiome research is a reason to use antibiotics wisely, not a reason to refuse them. Untreated bacterial infections can be dangerous, so if you're worried about your microbiome, talk to your doctor instead of stopping a prescription early.

3.9 Trying It Yourself: The Microbiome Balance

The simulation below is a cartoon gut community with 24 made-up species in five groups. Each dot stands for a small share of the community, the bar shows each group's share, and the chart tracks the diversity index over time. Opportunists (tomato red) are held in check by everyone else, which is colonization resistance in action.

Diagram: Microbiome Balance



Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch03-microbiome-balance/main.html

Open the Microbiome Balance fullscreen

MicroSim specification: Microbiome Balance

Type: microsim **sim-id:** ch03-microbiome-balance
Library: p5.js
Status: Implemented
Bloom Level: Apply
Bloom Verb: predict
Learning Objective: The learner will predict how an antibiotic course and a change in diet shift the diversity and makeup of a gut bacterial community, and explain why recovery is often partial and differs between people.

Canvas: 560 px drawing area plus 120 px controls (iframe 682 px); responsive down to about 320 px wide, where the panels stack.

Controls: Start/Pause, Reset (same starting person), New person (a different random starting community), Give antibiotic course (5 illustrative days), Diet select (Fiber-rich, varied plants; Low-fiber, high-sugar).

Rules: 24 species in 5 groups: fiber fermenters (Bacteroides-type), butyrate producers, Bifidobacteria, other commensals, and opportunists. Each group has a few abundant species and several rare ones. Commensals grow toward their own niche size; opportunists are held down by the size of the commensal community (colonization resistance). Antibiotics kill commensals quickly and opportunists slowly, so opportunists bloom for a while; each commensal species differs a little in how hard the drug hits it. Any species that falls below a "lost" threshold disappears and can't return on its own, so recovery is partial. A low-fiber diet shrinks the niches of rare fiber specialists most, shifting the community toward a few groups and lowering diversity modestly; returning to fiber restores species that are still present.

Feedback: Dot field, stacked composition bar with percentages, diversity line chart with antibiotic days shaded, and a panel showing the day, diversity index, species present out of 24, and a message explaining what just happened.

Provenance: Section 3.8 (Dethlefsen and Relman 2011; Palleja et al. 2018), Section 3.7 (Buffie and Pamer 2013). The diet behavior is a simplified illustration, not drawn from a study in this chapter. Species, rates, and diversity values are illustrative.

First, predict: what will happen to the diversity index during an antibiotic course, and will it return to exactly where it started? Then press **Give antibiotic course**. Watch the opportunists bloom as the commensals shrink, then watch the commensals regrow and push the opportunists back down. Check the "Species present" count when the line levels off. Did any species disappear for good?

Next, press **New person** and give the same antibiotic course. Does this person lose the same number of species? Finally, reset and switch the diet to **Low-fiber, high-sugar** for a couple of months of simulated time, then switch back. Notice that the diet change shifts the makeup of the community more than it changes diversity, and that the change reverses when fiber returns, because no species was lost.

What this model leaves out

- A real gut has hundreds of species and many more strains, plus archaea, fungi, and viruses, not 24 made-up species in five groups.
- Real antibiotics differ a lot: each one hits different bacteria, and effects vary by drug, dose, and person. The sim uses one generic course, and its opportunist bloom and species losses are rough cartoons.
- Real people pick up new microbes from food, other people, and the environment, so lost species can sometimes return; the sim doesn't allow that.
- The sim ignores the immune system, the gut lining, medicines other than antibiotics, and the person's health.
- Days, rates, diversity values, and the size of the diet effect are made up; they show patterns, not predictions for any real person.

3.10 Reading a Microbiome: 16S and Metagenomic Sequencing

For most of the history of microbiology, scientists studied bacteria by growing them in dishes. But many gut microbes are anaerobes with picky needs, and they're hard to grow. A 2019 study by Strandwitz and colleagues noted that, at the time, an estimated 23 to 65% of species in the human gut had never been grown in the lab. So researchers turned to reading DNA instead.

There are two main approaches, and you'll see both in research papers.

16S rRNA sequencing is a method for identifying bacteria in a sample by reading the DNA of one marker gene, the 16S ribosomal RNA gene, which all bacteria have and which differs between groups. It works like reading the barcode on a product: you can tell roughly what's on the shelf and how much of each, but not what each product can do. It is fast and relatively cheap, but it often can't tell apart closely related species or strains, and it only covers bacteria and archaea.

Metagenomic sequencing (also called shotgun metagenomics) is a method that reads fragments of *all* the DNA in a sample, from every organism present, so researchers can identify microbes in more detail and see which genes, and so which possible functions, are present. A 2017 review by Quince and colleagues says shotgun metagenomics has transformed microbiology. It's like reading every page of every book in a library instead of just the titles. The TEDDY study used both methods, and the Palleja antibiotic study used metagenomics.

	16S rRNA sequencing	Metagenomic sequencing
What it reads	One marker gene	All DNA in the sample

	16S rRNA sequencing	Metagenomic sequencing
Everyday comparison	Reading product barcodes	Reading every page in the library
Tells you	Which groups of bacteria are present, and in what proportions	Species and often strains, plus which genes (possible functions) are present
Limits	Less detail; usually can't see genes or functions	More expensive; needs more computing; genes present doesn't mean genes active

Both methods share a big limit: a stool sample shows what's leaving the colon, not exactly what's living along the whole gut wall. A 2018 review of best practices by Knight and colleagues stresses that choices about how samples are collected, stored, and analyzed can change the results.

This brings us back to Sam's cousin and the home gut test kit. These tests usually use one of the methods above on a stool sample, then send a report full of colorful charts, scores, and sometimes food or supplement suggestions.

Hype Meter: "A home microbiome test can tell you what to eat to improve your mood"

Strong | Moderate | Preliminary | **Hype**

Verdict: Hype. The sequencing itself can be real science, but a 2024 international consensus statement by dozens of microbiome experts (Porcari and colleagues, *Lancet Gastroenterology & Hepatology*) concluded that evidence for using gut microbiome tests in clinical care is scarce, and that direct-to-consumer tests are sold without agreed regulation or any proven clinical value. No one has defined what a "healthy" microbiome looks like (Section 3.11), so there is no validated standard to compare your sample to, and no trials show that following a kit's advice improves mood. **What would change the grade:** Validated reference ranges for specific microbiome features, plus randomized trials showing that test-guided diet changes improve a specific health outcome compared with general advice, could move a specific test up.

3.11 Dysbiosis and Defining a Healthy Microbiome

You'll often read that a disease is linked to "dysbiosis." **Dysbiosis** is a term for a change in the gut microbiota away from its usual makeup that is thought to be harmful, such as lower diversity, loss of beneficial groups, or overgrowth of potentially harmful ones. It's a useful word, but scientists warn that it's slippery.

The problem is in the definition. To say a microbiome has gone "wrong," you need to know what "right" looks like. **Defining a healthy microbiome** is the scientific challenge of identifying which features of a gut microbial

community reliably support health, and what their normal ranges are, given that healthy people's microbiomes differ greatly. A 2016 review by Lloyd-Price, Abu-Ali, and Huttenhower describes cataloguing the features of the microbiome that support health as an essential first step that is still underway. So far, no one has defined a single "healthy microbiome," and two healthy people can have very different communities, just like two healthy rainforests.

A 2020 essay by Harald Brüssow lists more problems. Many studies that compare people with a disease to people without it are too small, and some reported "dysbiosis" patterns don't repeat in other studies. Even the most advanced statistics explain only a small share of why microbiomes differ between people. And there's a circular trap: if we define dysbiosis as "the microbiome people with this disease have," we can't then use dysbiosis to explain the disease.

If you're going through this

If you have a gut condition or needed several rounds of antibiotics, it's easy to worry that you've "broken" your microbiome, especially after scrolling past posts about it. Remember that gut communities are resilient, that no one has defined a single healthy microbiome to measure yourself against, and that your care team treats your actual symptoms and test results, not a stool-test score. If you have questions about your microbiome and your condition, write them down and bring them to your next appointment.

3.12 Animal Models, Germ-Free Mice, and Correlation vs Causation

How do scientists test whether microbes *cause* something, rather than just showing up alongside it? Often, they start with animals.

An **animal model** is a non-human animal, such as a mouse or rat, used to study a biological process or disease because it shares important features with humans and can be studied in ways that aren't possible in people. Animal models let researchers control diet, genes, and environment, and run experiments that would be unethical in humans. The catch is that mice aren't small people: they eat differently, have different gut anatomy, and carry different microbes.

The most powerful microbiome model is the **germ-free mouse**, a mouse raised in a sterile isolator from birth so that it has no microorganisms at all, in or on its body, which lets researchers add specific microbes and watch what changes. A 2016 review by Luczynski and colleagues calls germ-free mice some of the most persuasive evidence that gut microbes affect the brain and behavior. A classic example: in 2004, Sudo and colleagues found that germ-free mice had an exaggerated stress-hormone response, and that giving them gut bacteria early in life partly corrected it, but giving bacteria later didn't. (Chapter 7 returns to this study.)

But the same Luczynski review warns that growing up germ-free causes permanent differences in how the brain and body develop. A germ-free mouse isn't a normal mouse minus its microbes; it's a different animal in many ways. And no human lives germ-free. So germ-free results suggest what microbes *can* do, not what they *do* in people.

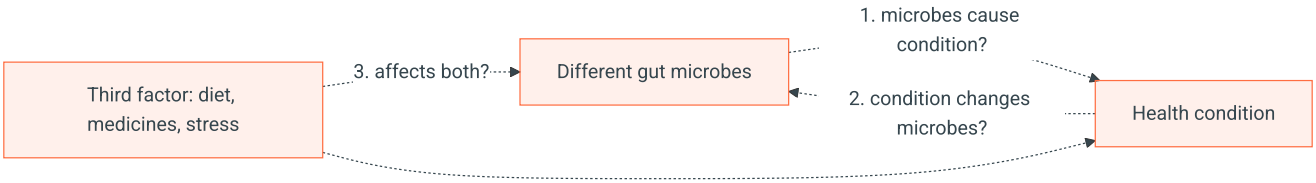
This part is tricky, and it matters



Correlation versus causation is the single most useful idea in this whole book, and it takes practice. If it feels confusing now, that's normal. You'll use it in nearly every chapter, and it gets easier each time.

Correlation vs causation is the distinction between two things happening together (a correlation, or association) and one thing actually producing the other (causation). Most microbiome studies in people are correlations: they find that people with a condition have different gut microbes. There are at least three ways that can happen:

1. **The microbes help cause the condition.** This is the exciting possibility.
2. **Reverse causation: the condition changes the microbes.** Diarrhea, inflammation, and changes in eating during illness all reshape the gut community.
3. **A third factor (a confounder) changes both.** Diet, medicines (including antibiotics), stress, sleep, and where someone lives can all affect both the microbes and the condition.



Researchers try to test cause with experiments. One common design is to transplant gut microbes from people with a disease into germ-free mice or rats and see whether the animals develop disease-like features. But a 2020 review in *Cell* by Walter and colleagues raised a warning. In their systematic review, 95% of published studies of this kind (36 of 38) reported that the disease-like trait transferred to the animals, and many then made causal claims about human disease. The authors argued that such a high success rate is implausible and overstates the microbiome's role in human disease. When almost every experiment "works," it may mean the method is biased, not that the microbes always matter.

Back to Riya. Studies find that people with Crohn's disease, on average, have different gut microbes than people without it. Riya now knows to ask: did the microbes help cause the disease, did the inflammation and medicines change the microbes, or both? Researchers think it's likely a two-way street, which Chapters 9 and 11 explore.

At the Bedside: Diarrhea During a Course of Antibiotics

Meet the patient (fictional)

Leah is 15 and plays club soccer. She had a sinus infection that didn't clear up, so her doctor prescribed an antibiotic. On day 4 she starts having loose stools a few times a day, with mild cramps. She has no fever and no blood in her stool, and she's still eating and drinking. Her mom calls the doctor's office, and Leah privately worries that she has "ruined" her gut bacteria forever.

What the doctor checks: The nurse asks how many loose stools Leah is having, whether there is fever, blood or mucus in the stool, severe belly pain or tenderness, signs of dehydration (dizziness, very little urine, a dry mouth), and whether she has had antibiotics or *C. difficile* before. Because her symptoms are mild and she has none of these warning signs, the doctor decides she doesn't need tests right now but gives clear instructions to call back if anything changes.

Connecting the signals: The antibiotic is killing the bacteria causing Leah's sinus infection, but it's also knocking down commensal bacteria in her colon. With fewer residents, her gut handles food and fluid differently, and colonization resistance is weaker for a while. That's the "antibiotic disruption" pattern from Section 3.8 and the sim.

Diagnosis: Mild antibiotic-associated diarrhea.

Why it happens: Antibiotics can't tell harmful bacteria from helpful ones. As the commensal community shrinks and shifts, the colon's normal work changes, and opportunists have more room. In most healthy people, the community regrows over the following weeks. The more serious version is *C. difficile* infection, which the CDC links to antibiotics: people are up to 10 times more likely to get it during and in the month after taking one. Warning signs that need a prompt call to a doctor include fever, many watery stools a day, stomach tenderness or pain, loss of appetite, nausea, blood in the stool, or diarrhea that continues after the antibiotic ends.

The mind-body side: Leah's biggest worry isn't the diarrhea; it's the idea that she has permanently damaged her body. The doctor explains that gut communities usually recover well, that the infection needed treatment, and that a few days of loose stools is a common, temporary side effect. The doctor also notes that worry can make the gut feel worse, and that it's fine to tell her coach she needs easy bathroom access for a few days.

Treatment today: For mild antibiotic-associated diarrhea, the doctor's plan is usually to keep drinking fluids and to finish the antibiotic as prescribed unless the doctor changes it. If the diarrhea is severe or warning signs appear, the doctor may test for *C. difficile* and may switch or stop the antibiotic. Leah shouldn't stop the medicine or add products on her own; any change is the doctor's call.

What's new in research: For adults whose *C. difficile* infection keeps coming back, doctors now have microbiome-based medicines. On April 26, 2023, the FDA approved Vowst, a fecal microbiota product (made from donated human stool) taken by mouth as capsules, to prevent *C. difficile* infection from coming back in adults 18 and older after antibiotic treatment for recurrent infection. In its placebo-controlled trial, the infection came back within 8 weeks in 12.4% of people taking Vowst versus 39.8% taking placebo. An earlier product, Rebyota (given rectally), was approved for the same use in November 2022. **Evidence grade: Strong**

for that specific use in adults. Neither product is approved for children, for a first *C. difficile* infection, or for any mental-health condition.

Your turn: reason through a variation

Leah's teammate Jordan took the same antibiotic a month ago. Now, three weeks after finishing it, he has many watery stools a day, a fever, and belly tenderness. Should he treat this as the same mild, temporary side effect? Why or why not?

Answer: No. Jordan's symptoms started after the antibiotic ended and include fever, frequent watery stools, and tenderness, which are warning signs. The CDC notes the risk of *C. difficile* stays raised for about a month after an antibiotic, and its symptoms include fever, diarrhea, and stomach tenderness. Jordan should contact a doctor promptly so they can check for *C. difficile* or another cause.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: All bacteria are bad, so fewer bacteria in your body is better.
Reality: Most gut bacteria are commensals that cause no harm, and many help, for example by fermenting fiber and by crowding out pathogens (colonization resistance). Only some bacteria, and some strains, cause disease.

Myth: Bacteria outnumber your human cells 10 to 1, so you're only 10% human.
Reality: A careful 2016 estimate found about 38 trillion bacteria and 30 trillion human cells in a typical adult, about 1.3 to 1. The old "10 to 1" figure is wrong.

Myth: There is one healthy microbiome, and a test can tell you if yours matches it.
Reality: Healthy people have very different gut communities, and scientists haven't defined a single healthy microbiome. Experts say direct-to-consumer microbiome tests have no proven clinical value.

Myth: If something happens in germ-free mice, it happens in people.
Reality: Germ-free mice grow up with permanent developmental differences, and mice differ from humans in diet, anatomy, and microbes. Germ-free results show what microbes *can* do in mice; human studies are needed to know what they do in people.

Myth: If people with a disease have different microbes, the microbes caused the disease.
Reality: That's a correlation. The disease or its treatments could have changed the microbes, or a third factor such as diet or medicines could affect both. Showing cause takes experiments, and even mouse transplant experiments can overstate cause.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Your gut bacteria outnumber your cells 10 to 1. That means your microbes are really in charge of your mood. Take our 30-strain probiotic to take back control!"

Grade: Hype. The first claim is wrong: the best estimate is about 1.3 bacteria per human cell, not 10. Even a true ratio wouldn't show that microbes control mood; that's a separate question, and the strongest evidence for microbe effects on behavior comes from germ-free mice, which don't translate directly to people. The ad also ends with a product, which is a reason to read twice as carefully. A careful version would say: "Your gut contains roughly as many bacterial cells as human cells, and researchers are studying whether and how they affect the brain."

2. Predict: Sam takes a 10-day antibiotic course for strep throat. Predict what happens to the diversity of his gut bacteria during the course and over the next two months.

During the course, diversity should drop and the makeup of his community should shift, with some groups shrinking and some opportunists growing, as in the Dethlefsen and Palleja studies. After the course, most of the community should regrow over weeks, with diversity returning close to where it started. But recovery may not be perfect: a few species might stay missing for months, and the exact pattern will differ from other people's.

3. Explain: Why are people more likely to get C. difficile infection during and after a course of antibiotics?

Normally, the commensal bacteria in the colon provide colonization resistance: they take up space and nutrients and make it hard for *C. difficile* to multiply. Antibiotics knock down many of those commensals, so *C. difficile* has room to grow and make people sick. The CDC says people are up to 10 times more likely to get it while taking an antibiotic and in the month after.

4. Apply: A study finds that teens with anxiety have lower gut microbial diversity than teens without anxiety. List three possible explanations.

First, lower diversity might contribute to anxiety (microbes affecting the brain). Second, reverse causation: anxiety could change eating, sleep, and gut movement, which then change the microbes. Third, a confounder: something like diet, a recent antibiotic, poor sleep, or a medicine could affect both anxiety and microbes. The study alone can't tell these apart; an experiment or a long-term study tracking the order of changes would help.

5. Read the data. In the 2018 Palleja study (Section 3.8), researchers followed 12 healthy young men after a 4-day course of three antibiotics. Here are key findings from the published abstract:

Measure	Finding
Number of participants	12 healthy men
Antibiotic course	4 days, 3 antibiotics together (meropenem, gentamicin, vancomycin)
Right after treatment	Opportunist bacteria bloomed; *Bifidobacterium* and butyrate producers dropped
Time to near-baseline makeup	About 1.5 months
Common species still undetectable in most men at 180 days	9

5. What does this data show, and what can't it show?

It shows that in healthy young men, the gut community largely recovered within about 1.5 months after a strong antibiotic course, but some species stayed missing for at least 6 months. It can't tell us whether the same happens in women, children, older adults, or people with gut diseases, or after a typical single antibiotic, because all 12 participants were similar and got an unusual three-drug course. It also can't show whether losing those 9 species affected health. A helpful follow-up would study a more varied group taking common antibiotics and measure health outcomes as well as microbes.

Exercises

Remember

1. What is the difference between the gut microbiota and the microbiome?

Answer

The gut microbiota is the community of microorganisms living in the gut. The microbiome is the microbiota plus their genes, the molecules they make, and the environment they live in.

1. According to Sender, Fuchs, and Milo (2016), about how many bacterial cells and human cells does a typical adult have?

Answer

About 38 trillion bacterial cells and about 30 trillion human cells, a ratio of about 1.3 to 1.

Understand

1. Explain why exclusively breastfed babies having lower gut diversity is not a sign of an unhealthy microbiome.

Answer

Human milk oligosaccharides feed a few groups of milk-loving bacteria, such as *Bifidobacterium*, so the infant community is dominated by those groups. This is a normal stage of microbiome development; diversity rises after breastfeeding stops. "More diversity is better" doesn't apply to healthy infants.

1. Explain how colonization resistance protects against infection, using a comparison of your own.

Answer

The normal residents of the colon use up space and nutrients and make substances that block invaders, so a newcomer like *C. difficile* struggles to settle in. One comparison: a full parking lot leaves no space for a newcomer's car. When antibiotics empty the lot, invaders can park.

Apply

1. Use the Microbiome Balance sim. Give an antibiotic course to three different "new people" and record the lowest diversity index, the diversity index 100 days later, and the number of species lost for each. Describe what's the same and what differs, and connect your results to the Dethlefsen and Relman finding that responses differed between people.
2. A friend's younger brother was born by C-section, and the friend says, "That's why he gets sick more. His microbiome was ruined at birth." Use the evidence in Section 3.6 to write a kind, accurate reply.

Analyze

1. Compare a 16S rRNA sequencing study and a metagenomic sequencing study of the same stool samples. What questions could the metagenomic study answer that the 16S study couldn't? What would both still be unable to tell you?
2. Walter and colleagues found that 36 of 38 studies transplanting human gut microbes into germ-free rodents reported that a disease-like trait transferred. Analyze why such a high success rate might make

scientists more skeptical, not less.

Evaluate

1. A company advertises: "Our microbiome test compares your gut to the healthy microbiome and gives you a personalized plan." Evaluate this claim using the concepts of defining a healthy microbiome, 16S versus metagenomic sequencing, and the 2024 expert consensus statement.
2. Judge this headline: "Antibiotics permanently destroy gut bacteria, study finds," written about the Palleja 2018 study. What does the headline get right, what does it get wrong, and how would you rewrite it?

Create

1. Design a study to test whether a common antibiotic used for teen ear or sinus infections changes gut diversity, and whether diversity fully recovers. Describe who you'd include, what you'd measure and when, what comparison group you'd use, and how you'd handle diet as a possible confounder.
2. Create a one-page "Microbiome myths vs facts" handout for a middle-school health class, covering at least four ideas from this chapter (for example, the bacteria-to-human cell ratio, commensals and pathogens, antibiotics, and home test kits), each with a one-sentence evidence grade.

Key Takeaways

- The gut microbiota is the community of microbes in your gut; the microbiome adds their genes, molecules, and environment. Most gut bacteria live in the colon.
- A typical adult has roughly 38 trillion bacterial cells and 30 trillion human cells, about 1.3 to 1. The old "10 to 1" figure is wrong.
- Most gut bacteria are commensals. Strains of the same species can behave very differently, and pathogens or opportunists can take advantage when the community is disturbed.
- Birth mode, breastfeeding, and human milk oligosaccharides shape a baby's first microbes; early birth-mode differences are real but fade over the first year or so.
- A healthy community provides colonization resistance. Antibiotics cause fast drops in diversity; most of the community recovers within weeks to months, but recovery can be incomplete and varies between people.
- Scientists read microbiomes with 16S rRNA sequencing (one marker gene) or metagenomic sequencing (all DNA). No single healthy microbiome has been defined, and home tests have no proven clinical value.
- Germ-free mice and other animal models show what microbes can do, but they don't translate directly to people, and most human microbiome findings are correlations, not proof of cause.

You've met the neighbors!



You can now count the microbes correctly, track how they settle in and bounce back, and spot when a study shows correlation instead of cause. Next, in Chapter 4, we'll see how the gut's immune system acts like a sense organ that can change how you feel.

Quiz: Meet the Microbiome

Test your understanding of Chapter 3. Choose the best answer, then click **Show Answer** to check.

Question 1

According to the 2016 estimate by Sender, Fuchs, and Milo, how do bacterial cells compare with human cells in a typical adult?

A. Bacteria outnumber human cells about 10 to 1.

B. Human cells outnumber bacteria about 10 to 1.

C. There are roughly as many bacterial cells as human cells, about 1.3 to 1.

D. Bacteria make up about half of the body's weight.

Show Answer

The correct answer is **C**. The estimate is about 38 trillion bacteria and 30 trillion human cells, roughly 1.3 to 1. Option A is the old "10 to 1" figure, which the 2016 analysis showed is wrong. The bacteria weigh only about 0.2 kilograms in total, so D is also wrong.

Concept Tested: Bacteria-to-Human Cell Ratio **Bloom's Level:** Remember

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Question 2

What is a bacterial strain?

A. A genetic variant within one bacterial species that can behave differently from other variants

B. A large group of bacteria, such as Firmicutes or Bacteroidetes

C. Any bacterium that causes disease

D. A virus that infects bacteria

Show Answer

The correct answer is **A**. Strains of one species share most genes but differ in some, which can change what they do. *E. coli* is the classic example: most strains are harmless, but some cause illness. Option B describes a phylum, a much larger group.

Concept Tested: Bacterial Strain **Bloom's Level:** Remember

Question 3

Which method reads fragments of all the DNA in a stool sample, so researchers can see which genes are present?

A. 16S rRNA sequencing

B. Growing bacteria on lab dishes

C. Counting bacteria under a microscope

D. Metagenomic (shotgun) sequencing

Show Answer

The correct answer is **D**. Metagenomic sequencing reads DNA from every organism in the sample, revealing species, often strains, and possible functions. 16S rRNA sequencing (A) reads only one marker gene, so it identifies groups of bacteria but usually not their genes.

Concept Tested: Metagenomic Sequencing **Bloom's Level:** Remember

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Question 4

Why does a healthy gut community make it harder for *C. difficile* to cause infection?

A. Commensal bacteria make antibiotics that kill all pathogens.

B. Resident bacteria take up space and nutrients and block invaders, a protection called colonization resistance.

C. *C. difficile* can only live in the stomach, not the colon.

D. Healthy people's immune systems destroy every bacterium that enters the gut.

Show Answer

The correct answer is **B**. Colonization resistance works like a full parking lot: when commensals already use the space and food, a newcomer struggles to settle in. That's why antibiotics, which knock down commensals, raise the risk of *C. difficile*. Option D is wrong because the gut normally hosts trillions of bacteria.

Concept Tested: Colonization Resistance **Bloom's Level:** Understand

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Question 5

Exclusively breastfed babies have lower gut diversity in their first 6 months. What is the best interpretation?

A. Breastfeeding damages the infant microbiome.

B. These babies are likely to get sick more often.

C. It's normal: human milk oligosaccharides feed a few milk-loving groups, so those groups dominate early on.

D. It shows that more diversity is always healthier.

Show Answer

The correct answer is **C**. Human milk oligosaccharides are sugars the baby can't digest that feed certain bacteria such as *Bifidobacterium*, so a few groups dominate. This is a normal stage of microbiome development. Option D is the misconception the breastfeeding data disproves.

Concept Tested: Human Milk Oligosaccharides **Bloom's Level:** Understand

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Question 6

Why does this book warn against applying germ-free mouse results directly to people?

A. Growing up germ-free causes permanent developmental differences, and mice differ from humans in many ways.

B. Germ-free mice actually carry more microbes than normal mice.

C. Germ-free mice have never been used in microbiome research.

D. Mouse experiments can never show cause.

Show Answer

The correct answer is **A**. Germ-free mice are powerful for testing what microbes can do, but they develop differently from normal mice, and no human lives germ-free. Option D is wrong: mouse experiments can test cause, but only in mice.

Concept Tested: Germ-Free Mouse **Bloom's Level:** Understand

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Question 7

Leah, 15, is taking an antibiotic for a sinus infection and has mild loose stools on day 4, with no fever or blood. Based on the human studies in this chapter, what is most likely happening to her gut bacteria?

A. Her gut bacteria are permanently destroyed and will never recover.

B. The antibiotic is only affecting her sinuses, so her gut bacteria are unchanged.

C. Her gut bacteria have all been replaced by *C. difficile*.

D. Diversity has dropped, and most of the community will likely regrow over the following weeks, though recovery may not be perfect.

Show Answer

The correct answer is **D**. Human studies show antibiotics quickly reduce gut diversity, and most of the community regrows within weeks to a couple of months, sometimes with a few species missing. Option A is the "ruins forever" Hype claim; mild symptoms without warning signs don't suggest *C. difficile* (C).

Concept Tested: Antibiotic Disruption **Bloom's Level:** Apply

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Question 8

A company says its home test "compares your gut to the healthy microbiome." Which fact from this chapter best challenges that claim?

A. Stool samples can't be sequenced.

B. No single healthy microbiome has been defined, and healthy people's microbiomes differ greatly.

C. Bacteria outnumber human cells 10 to 1.

D. Only 16S sequencing is allowed in home tests.

Show Answer

The correct answer is **B**. Without an agreed definition of a healthy microbiome, there's no validated standard to compare a sample to, and a 2024 expert consensus found no proven clinical value for direct-to-consumer tests. Option A is wrong; stool can be sequenced, but the results can't be compared to a standard that doesn't exist.

Concept Tested: Defining a Healthy Microbiome **Bloom's Level:** Apply

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Question 9

A study finds that people with a gut disease have lower microbial diversity than healthy people. Which explanation can this study alone NOT rule out?

A. That the disease and its treatments changed the microbes

B. That diet or medicines affected both the microbes and the disease

C. Both of these, because it shows a correlation, not cause

D. Neither, because lower diversity always causes disease

Show Answer

The correct answer is **C**. A difference between groups is a correlation. Reverse causation (the disease changes the microbes) and confounding (a third factor affects both) remain possible until experiments or careful long-term studies test them. Option D treats correlation as proof of cause.

Concept Tested: Correlation vs Causation **Bloom's Level:** Analyze

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Question 10

Walter and colleagues found that 36 of 38 studies transplanting human gut microbes into germ-free rodents reported that a disease trait transferred. Why did they see this as a warning sign?

A. Such a high success rate is implausible and suggests the method or reporting overstates the microbiome's role.

B. It proves the microbiome causes almost every human disease.

C. It shows that germ-free rodents can't be used in research.

D. It means human studies are no longer needed.

Show Answer

The correct answer is **A**. When nearly every experiment "works," it may reflect bias in methods or in which results get published, not a true causal role in humans. The authors argued for more rigorous tests of cause. Option B is exactly the overreach they warned against.

Concept Tested: Animal Model **Bloom's Level:** Analyze

Chapter 4: The Immune System as a Sense Organ

Summary

Your immune system does more than fight germs. It constantly samples what is in your gut, decides what is safe and what is dangerous, and reports back to the brain using chemical messengers called cytokines. This chapter tours the gut's border wall (the lining, its mucus, and the seals between cells), the immune tissue that samples what you swallow, and the alarm system of inflammation. It then follows immune messages to the brain by four routes, meets the brain's own immune cells, and explains why being sick makes you tired, hungry for nothing, and low. Finally, it grades the evidence linking inflammation to depression and busts the popular claim that "70% of your immune system is in your gut."

Concepts Covered

1. Innate Immunity
2. Adaptive Immunity
3. Intestinal Epithelium
4. Mucus Layer
5. Tight Junction
6. Gut-Associated Lymphoid Tissue
7. Pattern Recognition Receptor
8. Inflammation
9. Cytokine
10. Interleukin-6
11. Tumor Necrosis Factor
12. Interleukin-1 Beta
13. Regulatory T Cell
14. Immune-to-Brain Signaling
15. Circumventricular Organ
16. Microglia
17. Neuroinflammation
18. Sickness Behavior

Prerequisites

- Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading) for the gut wall layers and the Hype Meter
- Chapter 2: The Vagus Highway for afferent (upward) vagus signals and the brainstem
- Chapter 3: Meet the Microbiome for gut microbes, germ-free mice, and correlation vs causation

Why being sick feels the way it does



Every time you've had the flu and wanted nothing but your bed, your immune system was talking to your brain, and I carried some of those messages myself. This chapter explains that conversation, which matters most for people like Riya, whose gut inflammation can make them exhausted and low. It also gives you the tools to see through one of the most repeated numbers on the internet. Let's check what the gut is really telling the brain!

4.1 Why Does Riya Feel So Drained?

Last winter, Sam caught the flu two days before a cross-country meet. He had a fever, his muscles ached, and food sounded disgusting. What surprised him most was his mood. He didn't want to text anyone, his favorite shows seemed boring, and he slept twelve hours and still woke up tired. "I felt like a different person," he told Riya when he came back to school. (Sam and Riya are fictional students who appear throughout this book.)

Riya knew exactly what he meant. During a Crohn's flare, the same fog settles over her: deep tiredness, no appetite, a heavy, flat mood, and a wish to skip orchestra and hide in her room. For a long time she worried that this meant she was lazy or "being dramatic." At her last visit, her pediatric gastroenterologist, Dr. Alvarez, told her something that changed how she saw it: "That tiredness is not a character flaw. Inflammation in your gut sends signals to your brain, and your brain responds by making you want to rest." This chapter is about those signals. They are real and measurable, and scientists have a name for what they do: sickness behavior.

If you're going through this

If inflammation leaves you wiped out, you are not imagining it and you are not weak. Fatigue is one of the most common symptoms people with inflammatory bowel disease report, and it deserves to be taken as seriously as pain or diarrhea. Tell your care team when tiredness or low mood shows up, even if your gut symptoms seem mild, because there are often things they can check and help with. It's also okay to tell teachers or coaches, "My condition can make me very tired some days."

4.2 A Security System That Also Sends Reports

Before any technical words, picture a large airport. At every gate, security officers check what comes through. They know the look of normal luggage, and they react fast to anything suspicious. Some officers are generalists who respond to anything odd; others are specialists trained to recognize one particular threat. When something goes wrong, they don't only deal with it at the gate. They radio headquarters, and headquarters changes how the whole airport runs: flights slow down, extra staff are called in, and announcements go out.

Your immune system works a lot like that. Its cells sit at the body's borders, especially the gut, sample what arrives, sort harmless from harmful, and respond. And, like the officers radioing headquarters, they send chemical reports to the brain that change how you feel and act.

That is why this chapter calls the immune system a "sense organ." Your eyes detect light; the immune system detects microbes, damaged cells, and danger signals. A 2021 review in the journal *Science* by Agirman, Yu, and Hsiao describes both the brain and the gut as key sensory organs, with immune cells constantly surveying their surroundings and signaling inflammation across the gut-brain axis. "Sense organ" is a way of thinking, not an official category in anatomy books, but it captures something true: the immune system gathers information about your inner world and passes it on.

4.3 Two Teams: Innate and Adaptive Immunity

Biology classes usually split the immune system into two teams that work together. The open textbook *Anatomy and Physiology 2e* from OpenStax describes them this way.

Innate immunity is the fast, general part of the immune system that you are born with. It responds within minutes to hours to broad signs of trouble, such as pieces of bacterial walls or chemicals released by damaged cells, and it reacts the same way each time. Physical barriers like skin and the gut lining, plus cells such as macrophages ("big eaters" that swallow microbes) and neutrophils, are part of this team.

Adaptive immunity is the slower but highly specific part of the immune system, run by white blood cells called lymphocytes (T cells and B cells). It learns to recognize particular invaders, takes days to ramp up the first time, and keeps a memory, so it responds faster the next time. B cells can become plasma cells, which make antibodies, proteins that latch onto a specific target.

Feature	Innate immunity	Adaptive immunity
Speed	Minutes to hours	Days the first time, faster later
What it recognizes	Broad patterns shared by many microbes	One specific target
Memory	No	Yes
Example cells	Macrophages, neutrophils, dendritic cells	T cells, B cells, plasma cells

Feature	Innate immunity	Adaptive immunity
Airport comparison	Generalist officers	Specialist officers

The two teams constantly hand off information. Dendritic cells, for example, are innate cells that grab samples of microbes and carry them to lymphoid tissue, where they "show" those samples to T cells and start an adaptive response. You'll see that hand-off happen in the gut in Section 4.5.

4.4 The Gut's Border Wall

Food and microbes in the gut tube are separated from your blood and tissues by a lining only one cell thick, the surface of the mucosa you met in Chapter 1.

Think of a castle wall with three parts: a muddy moat in front, a wall of tightly fitted stones, and mortar sealing the cracks between the stones.

Intestinal epithelium is the single layer of cells that lines the inside of the intestine and forms the barrier between the gut's contents and the body. Most of these cells (enterocytes) absorb nutrients. Others, called goblet cells, make mucus, and a few release hormones or antimicrobial chemicals. In the castle picture, the epithelium is the wall of stones. OpenStax describes the colon lining as a single layer of column-shaped cells made mostly of absorptive cells and goblet cells.

Mucus layer is the slippery gel, made mostly of large proteins called mucins, that coats the intestinal epithelium and keeps most microbes at a distance. It is the moat. In 2008, Johansson, Hansson, and colleagues showed in **mice** that the colon's mucus has two layers: a dense inner layer, firmly attached to the lining, that bacteria could not get into, and a looser outer layer where bacteria live. Mice bred without the main mucus protein (called Muc2) had bacteria touching their gut lining and went on to develop colon inflammation. That is mouse evidence that the moat matters.

Tight junction is a seal made of proteins that links neighboring epithelial cells near their top edge and controls what can slip through the gaps between them. OpenStax describes tight junctions as the connection type that most tightly separates the cells' top surfaces from the rest of the tissue. In the castle picture, tight junctions are the mortar. They are not completely watertight; they let water and some small molecules pass, and the body can loosen or tighten them. (Chapter 6 covers "intestinal permeability" and the popular "leaky gut" claim in detail. For now, just know that the seal is adjustable, not a solid wall.)

Barrier part	Castle comparison	What it does
Mucus layer	Moat	Keeps most microbes away from the lining
Intestinal epithelium	Wall of stones	One-cell-thick lining that absorbs food and blocks invaders

Barrier part	Castle comparison	What it does
Tight junctions	Mortar between stones	Seal the gaps between lining cells; adjustable
Immune cells beneath	Guards behind the wall	Sample, sort, and respond to anything that gets through

Inside the tube is outside the body



Here's a mental trick I use: imagine a donut. The hole goes right through the donut but isn't part of the dough. Your gut tube is the donut hole, so the barrier between it and your body has a huge job.

4.5 Sampling Stations: Gut-Associated Lymphoid Tissue

A border wall that blocked everything would be useless; you need to absorb food and get along with trillions of helpful microbes (Chapter 3). So the gut has built-in sampling stations, places where immune cells deliberately take small samples of what is in the gut and decide whether to react.

Gut-associated lymphoid tissue (GALT) is the collection of immune tissue in the gut wall where immune cells sample what we swallow and organize responses. A 2021 review of human GALT by Mörbe and colleagues lists its main parts: the Peyer's patches of the lower small intestine (the ileum), the appendix, and many small, scattered clusters called isolated lymphoid follicles. The authors note that much of what we know comes from mice.

Peyer's patches are dome-shaped clusters of immune cells. OpenStax explains that they sit mostly in the last part of the small intestine and contain special lining cells called M cells (microfold cells), which pick up material from inside the gut and pass it to immune cells waiting underneath. Dendritic cells can also open tight junctions briefly and poke probes between lining cells to sample microbes, then carry what they find to nearby lymphoid follicles, where T cells inspect it. If a response is needed, the result is often a kind of antibody called IgA that is released into the gut.

Riya's Crohn's disease affects the end of her small intestine, the same region where Peyer's patches cluster. Treat that as an interesting overlap, not an explanation; scientists are still working out why Crohn's so often involves this area.

The "70%" number

You have probably seen the claim that "70% of your immune system is in your gut." It appears in ads, wellness posts, and even some textbooks. In 2023, a team led by Ron Sender and Ron Milo at the Weizmann Institute of Science published the most careful count yet, in the journal *PNAS*. They estimated that a reference adult's immune system contains about 1.8 trillion cells, weighing about 1.2 kilograms (about 2.6 pounds). Then they asked where those cells live.

The answer: the gut holds about 70% of the body's antibody-making plasma cells, but only about 3% of all immune cells. The popular claim that "70% of your immune system is in your gut" is not supported. Most of the body's lymphocytes live elsewhere, mainly in lymph nodes and the spleen. The same 2023 count found about 5% of lymphocytes in the gut, and an earlier cross-species review by Ganusov and De Boer (2007) had already estimated only 5% to 20%.

So where did 70% come from? It likely mixes up two different things: the share of one cell type (plasma cells) and the share of the whole immune system. One widely cited 2008 review states the 70% figure without giving a count behind it. The gut really is a major immune site, and the biggest home of antibody-making cells. It just isn't 70% of everything.

70% of what?



When I see a percentage, my first question is "70% of what?" Seventy percent of plasma cells and 70% of all immune cells sound alike, but the careful count shows they differ by more than twentyfold.

Hype Meter: "70% of your immune system lives in your gut"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. The most systematic count of human immune cells (Sender et al., 2023) found that the gut holds about 3% of all immune cells and about 5% of lymphocytes. What is true is that about 70% of antibody-making plasma cells are in the gut. The popular version turns a fact about one cell type into a claim about the whole system, often to sell a gut supplement. **What would change the grade:** A new, careful whole-body count by a different method that found most immune cells in the gut. The 2023 count and the earlier 2007 review point the opposite way, so this is unlikely.

4.6 Spotting Trouble and Sounding the Alarm

How does an immune cell know that something is dangerous? It doesn't recognize every microbe by name. Instead, the innate team watches for shapes that are common to many microbes but absent from your own healthy cells, like a security scanner that flags any object with the outline of a blade.

A **pattern recognition receptor** (PRR) is a protein on or inside an immune cell (and some other cells, including gut lining cells) that recognizes molecular patterns shared by many microbes, such as pieces of bacterial cell walls or the whip-like tails called flagella, and also molecules released by stressed or damaged cells. OpenStax describes PRRs as receptors that probably evolved before the adaptive immune system. The best-known family is the Toll-like receptors (TLRs). When a PRR detects a match, it switches on genes in the cell that start the alarm.

That alarm is inflammation. **Inflammation** is the body's protective response to infection or injury, in which blood vessels widen and become leakier, immune cells rush in, and the area becomes warm, red, swollen, and painful. OpenStax lists those four classic signs (heat, redness, pain, and swelling), notes that "loss of function" is sometimes added as a fifth, and points out that inflammation can start from tissue injury alone, without any infection.

Inflammation is not the enemy; it is how a cut heals and a stomach bug gets cleared. Problems arise when it is too strong, in the wrong place, or doesn't switch off, as in inflammatory bowel disease (Chapter 9). So the immune system needs brakes as well as an accelerator.

One important brake is the **regulatory T cell** (Treg), a type of T cell whose job is to calm down or suppress other immune responses, helping to prevent the immune system from attacking the body's own tissues or harmless things like food and friendly microbes. OpenStax notes that regulatory T cells carry marker proteins called CD25 and FOXP3, that they are the most recently discovered T cell type, and that exactly how they work is still being studied. What is clear is that they suppress other T cell responses. Researchers are very interested in how gut microbes might help train Tregs, but much of that work has been done in mice.

For families

It's easy to think of the immune system as something to "boost," but a teen with Crohn's disease or ulcerative colitis has an immune system that is already too active in the gut. That's why many of their medicines calm the immune system down rather than pumping it up. If relatives suggest "immune-boosting" supplements, it helps to explain this gently and suggest that any product be checked with the teen's care team first, since some can interact with treatment.

4.7 Cytokines: The Immune System's Text Messages

Once the alarm is raised, immune cells need to coordinate. They do it with chemical messages.

A **cytokine** is a small protein that cells release to send signals to other cells, especially to coordinate immune responses and inflammation. OpenStax describes cytokines as signaling molecules that let cells communicate over short distances, changing what the receiving cell does. Think of them as text messages: short, fast, and capable of telling the receiver to do something very different. Some cytokines turn inflammation up (pro-inflammatory cytokines) and others turn it down (anti-inflammatory cytokines).

A 2008 review by Robert Dantzer and colleagues in *Nature Reviews Neuroscience* names the main pro-inflammatory cytokines that act on the brain during infection: interleukin-1 (alpha and beta), tumor necrosis factor-alpha, and interleukin-6. You'll meet all three throughout this book.

Dantzer's review also explains that pro-inflammatory cytokines drive the whole-body side of inflammation: fever, changes in how the body uses fuel, and the liver's production of "acute phase" proteins. One of those liver proteins is C-reactive protein (CRP), which OpenStax describes as an early defense protein made in the liver. CRP is easy to measure in a blood sample, so doctors and researchers use it as a general marker of inflammation.

Interleukin-1 beta (IL-1β) is a pro-inflammatory cytokine released by activated innate immune cells, such as macrophages, early in an immune response. It helps coordinate local and whole-body inflammation and is one of the main cytokines linked to sickness behavior.

Interleukin-6 (IL-6) is a pro-inflammatory cytokine released during inflammation that travels in the blood and helps produce whole-body effects such as fever and the liver's acute phase response. Because IL-6 and CRP are easy to measure in blood, they show up in many human studies of inflammation and mood.

Tumor necrosis factor (TNF, often written TNF-alpha) is a pro-inflammatory cytokine, made by immune cells such as macrophages, that drives and sustains inflammation in tissues. Despite its odd name, its everyday job is coordinating inflammation. TNF matters a lot in gut medicine: drugs that block it, called anti-TNF biologics, are a mainstay of treatment for Crohn's disease. The first, infliximab, was approved by the FDA for Crohn's disease in 1998 and for ulcerative colitis in 2005. (Riya's biologic is one of several types of IBD medicine; Chapter 9 covers them.)

Cytokine	Main sources	Some jobs	Why it matters in this book
Interleukin-1 beta (IL-1β)	Macrophages and other innate cells	Early alarm, local and whole-body inflammation	Strongly tied to sickness behavior
Interleukin-6 (IL-6)	Immune cells during inflammation	Fever, liver's acute phase response (including CRP)	Common blood marker in human mood studies
Tumor necrosis factor (TNF)	Macrophages and other immune cells	Drives and sustains inflammation in tissues	Target of anti-TNF drugs for Crohn's disease

For the gut-brain axis, what matters is that these messengers don't stay at the scene. Dantzer's review explains that cytokines made in the body also act on the brain to cause the behavioral symptoms of sickness. So how does a protein made in your gut wall get its message into your head?

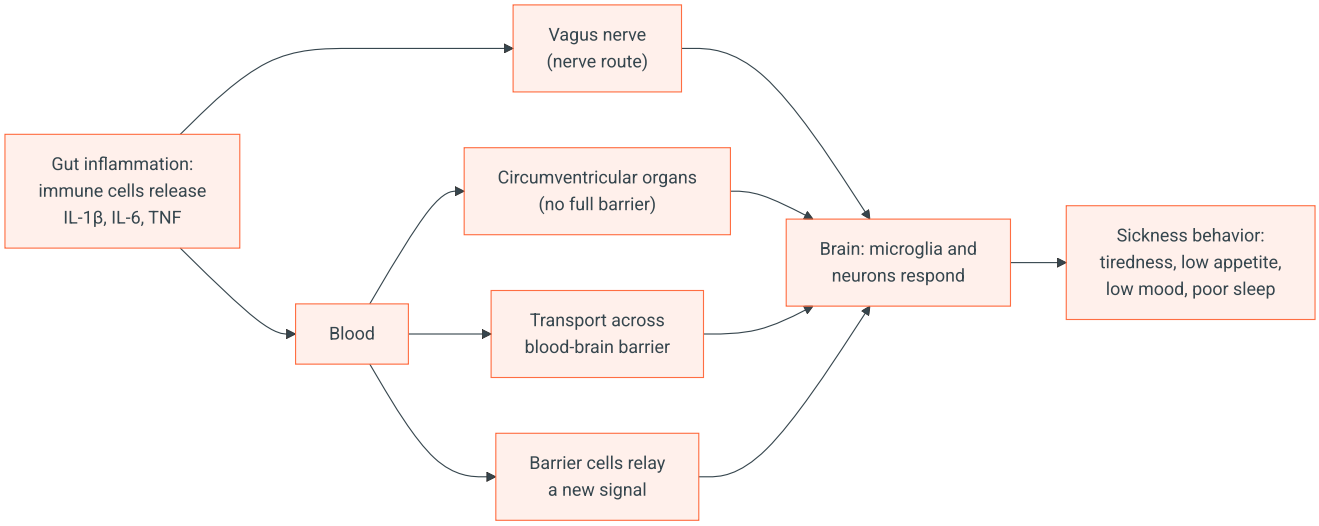
4.8 How Immune Messages Reach the Brain

The brain is protected by the blood-brain barrier, a tightly sealed layer of blood vessel cells that blocks most large molecules in the blood from entering brain tissue. (Chapter 5 covers it in detail.) Cytokines are fairly large proteins, so for a long time many people assumed the brain was simply sealed off from the immune system. It isn't.

Immune-to-brain signaling is the set of pathways by which messages from the immune system, especially cytokines, reach the brain and change its activity. A 2007 review by Ning Quan and William Banks listed four main routes. Most of the detailed evidence for each route comes from animal experiments, but together they are well accepted.

1. **The nerve route.** Cytokines released in the gut or belly activate sensory nerve fibers, especially those of the vagus nerve, which carry the alarm up to the brainstem. You met these upward (afferent) vagus signals in Chapter 2. Experiments in rats by Lisa Goehler and colleagues showed that immune cells near vagus nerve fibers release chemicals that activate those fibers. This is the fastest route.
2. **The leaky-window route.** A few small brain areas have no full blood-brain barrier, so blood-borne signals can reach brain tissue there.
3. **The transport route.** Some cytokines are carried across the blood-brain barrier by transport systems. A 2005 review by Banks, based largely on animal studies, stresses that not all cytokines are transported and that transport rates differ.
4. **The relay route.** The cells that make up the barrier have receptors for cytokines. When cytokines bind on the blood side, barrier cells release their own signals (such as prostaglandins, the chemicals that fever reducers block) on the brain side.

The "leaky windows" in route 2 have a name. A **circumventricular organ** is one of several small brain regions located around the fluid-filled spaces (ventricles) deep in the brain that lack a complete blood-brain barrier, letting them sample the blood directly. A 2017 review by Kaur and Ling describes them as midline structures around the third and fourth ventricles, defined by their lack of a blood-brain barrier. Dantzer's review adds that macrophage-like cells in the circumventricular organs have Toll-like receptors, so they can detect microbe patterns in the blood and make cytokines that then spread into nearby brain tissue.



Four routes, one message



Four routes can feel like a lot, so try remembering them as nerve, window, carrier, and relay. You don't need every detail; the big idea is that the brain has several back doors for hearing about inflammation, and I'm the fastest one.

The brain talks back

The conversation runs both ways. In 2002, Kevin Tracey described what he called the "inflammatory reflex" in the journal *Nature*. In animal experiments, signals traveling down the vagus nerve reduced the release of pro-inflammatory cytokines, meaning the nervous system can turn inflammation down in real time. On July 30, 2025, the FDA approved an implanted vagus nerve stimulator, the SetPoint System, for adults with moderate to severe rheumatoid arthritis who didn't respond to biologic or targeted drugs. It is not approved for Crohn's disease, IBS, or anxiety.

4.9 The Brain's Own Immune Cells: Microglia

Microglia are the brain's resident immune cells, a type of macrophage that lives permanently in the brain and spinal cord, constantly surveying its surroundings, clearing debris, pruning connections between neurons, and responding to injury or infection. If the blood-brain barrier is the airport fence, microglia are the security staff who live inside the terminal. Dantzer's review describes them as calmer than macrophages elsewhere in the body, but able to make pro-inflammatory cytokines when stimulated. (For a refresher on glia, the brain's non-neuron cells, see From Neuron to Bedside, Chapter 1.)

Microglia have an unusual origin. Most immune cells are constantly replaced by new cells from the bone marrow. But in 2010, Florent Ginhoux and colleagues used a method called fate mapping in **mice** to show that adult microglia come from early precursor cells formed in the embryo, before the bone marrow even exists, and that they settle in the brain and maintain themselves.

Microglia may also listen, indirectly, to gut microbes. In 2015, Daniel Erny and colleagues found that **germ-free mice** (raised with no microbes at all, as you learned in Chapter 3) had immature microglia that responded poorly to infection. Giving the mice short-chain fatty acids, chemicals that gut bacteria make from fiber, helped restore them. This is mouse evidence, and no person lives germ-free.

Hype Meter: "Your gut bacteria control your brain's immune cells"

Strong	Moderate	**Preliminary**	Hype

Verdict: Preliminary. In mice, the complete absence of gut microbes left microglia immature, and microbial chemicals (short-chain fatty acids) helped them recover (Erny et al., 2015). Whether normal differences in human gut microbes change human microglia in a meaningful way has not been shown. "Control" overstates even the mouse results, which show influence, not command. **What would change the grade:** Human studies, for example brain imaging or tissue studies linking specific microbial chemicals to microglial activity, ideally followed by trials that change those chemicals and track brain immune markers.

Neuroinflammation

When microglia and other brain cells switch into an alarm state, scientists call it neuroinflammation. **Neuroinflammation** is inflammation within the brain or spinal cord, involving activated microglia and other glia releasing cytokines and other inflammatory chemicals. It ranges from a brief, helpful response during an infection to a long-lasting state seen in conditions like multiple sclerosis.

Measuring neuroinflammation in living people is hard, because no one can take a sample of a healthy person's brain. One approach uses PET scans with a tracer that sticks to a protein called TSPO, which rises in activated microglia. In 2015, Elaine Setiawan, Jeffrey Meyer, and colleagues in Toronto scanned 20 people during a major depressive episode and 20 healthy volunteers. TSPO signal was about 26% to 33% higher in three brain regions in the depressed group, and higher signal in one region went with more severe depression. That is human evidence, but it is a small study that shows a correlation, not cause, and TSPO is an imperfect marker.

4.10 Sickness Behavior: A Strategy, Not a Weakness

Now we can return to Sam's flu and Riya's flare.

Sickness behavior is the coordinated set of changes in mood and behavior that occurs during infection or inflammation, including tiredness, sleepiness, loss of appetite, reduced interest in people and activities, trouble concentrating, and low mood, driven by immune signals acting on the brain. Dantzer's review describes it plainly: sick people tire easily, ignore food and drink, lose interest in the world around them, sleep poorly in fragments, and feel low and irritable.

It is easy to see this as simple weakness. In 1988, the veterinary scientist Benjamin Hart argued something different. Reviewing the research on sick animals and people, he proposed that sickness behavior is not a breakdown but an organized, evolved strategy that helps fever fight viral and bacterial infections. One way to picture it: by lying low, the body puts its effort into the fight. The idea is widely accepted, though parts of it are still theory. In this view, sickness behavior is less like a car running out of gas and more like a driver deciding to pull over.

Humans show it in experiments too. In 2010, Naomi Eisenberger, Michael Irwin, and colleagues at UCLA randomly assigned 39 healthy adults to receive either a placebo or a low dose of endotoxin, a piece of bacterial cell wall that safely triggers a short burst of inflammation. Compared with the placebo group, the endotoxin group reported a bigger drop in mood, and brain scans showed less activity in a reward area (the ventral striatum) while they waited for a chance to win money. Because people were randomly assigned, this was an experiment that tested cause: inflammation, by itself, lowered mood and dulled the brain's reward response for a few hours.

Inflammatory bowel disease shows the same pattern over a longer timescale. A 2022 meta-analysis by D'Silva and colleagues, combining 20 studies of adults with IBD, found that about 47% reported fatigue overall. Fatigue was reported by about 72% of people with active disease and 47% of people in remission. Sleep problems, anxiety, depression, and anemia (low red blood cells) were the risk factors most often linked to it, so inflammation is not the only cause.

Sick, not lazy



A common mistake is to call illness fatigue "all in your head." It does involve your head, since your brain produces the feeling, but it is triggered by real immune signals you can measure in the blood. "In the brain" and "imaginary" are not the same thing.

4.11 From Sickness to Low Mood: Is Inflammation Behind Depression?

If a few hours of inflammation lowers mood, what happens when inflammation lasts for months? Dantzer's 2008 review suggested that when immune activation continues without stopping, as in long infections, cancer, or autoimmune diseases, immune signaling to the brain can deepen sickness and lead to symptoms of depression in vulnerable people. Several kinds of human evidence support a link.

People with depression have higher inflammation markers, on average. A 2020 meta-analysis by Osimo and colleagues combined 107 studies including 5,166 people with depression and 5,083 people without. The depressed groups had higher average levels of CRP, IL-6, TNF, and other markers. But this is an average shift across groups. Many people with depression have normal inflammation levels, and the study can't say which came first.

Giving people a cytokine can trigger depression. A cytokine called interferon alfa was once used at high doses to treat some cancers and hepatitis, and depression was a common side effect. In a 2001 trial published in the *New England Journal of Medicine*, Dominique Musselman, Andrew Miller, and colleagues randomly assigned 40 people with melanoma (a skin cancer) who were about to start interferon to take an antidepressant or a placebo first. Over the first 12 weeks, depression developed in 2 of 18 people in the antidepressant group (11%) and 9 of 20 in the placebo group (45%). The placebo group shows how often a cytokine treatment alone led to depression.

Blocking a cytokine helps some people, not all. This is the most interesting test, and it uses the same drug class as many Crohn's treatments. We look at it closely in the box below.

Inflammatory diseases come with more depression symptoms. In adults with IBD, a 2021 meta-analysis of 77 studies (30,118 patients) found symptoms of anxiety in 32.1% and symptoms of depression in 25.2%, higher during active disease. (Those are questionnaire scores, not diagnoses, and Chapter 11 explores why living with a chronic illness also affects mood in ways that have nothing to do with cytokines.)

In 2013, Charles Raison, Andrew Miller, and colleagues at Emory University tested whether blocking TNF could treat depression. They enrolled 60 adults whose depression had not improved enough with standard treatment and randomly assigned them, double-blind, to three infusions of the anti-TNF drug infliximab or a placebo over a 12-week trial. Overall, infliximab did no better than placebo. But the effect depended on inflammation at the start. In people with high CRP (above 5 mg/L), symptoms tended to improve more with infliximab; in people with low CRP, they tended to improve more with placebo. In an exploratory look at the high-CRP group, 8 of 13 people on infliximab (62%) responded, compared with 3 of 9 on placebo (33%), a difference that could still have been chance.

How to read a gut-brain claim: the 2013 infliximab depression trial

Question	This study
Mouse or human?	Human: 60 adults with treatment-resistant major depression.
Correlation or cause?	Cause can be tested, because it was a randomized, double-blind, placebo-controlled trial. The main result was no overall effect; the high-inflammation finding came from a smaller subgroup analysis, which is weaker.
How many?	60 people (30 per group); only 22 had high CRP, so the subgroup was tiny.
How long?	12 weeks, with infusions at weeks 0, 2, and 6.
Who paid for it?	The National Institute of Mental Health and Centocor Ortho Biotec Services, the company that made infliximab, which also supplied the drug and placebo free of charge; plus NIH research-center grants.
Is something being sold?	Not to the public in this paper, but the drug's maker helped fund it. Infliximab is approved for Crohn's disease, ulcerative colitis, and other inflammatory diseases, not for depression.

The conclusion: anti-TNF treatment does not work for depression in general. It might help a subset of people with high inflammation, but that idea needs a larger trial designed to test it. This is a good example of science getting more precise. Instead of "inflammation causes depression," the better statement is "inflammation may contribute to depression in some people."

Hype Meter: "Inflammation causes depression"

Strong	**Moderate**	Preliminary	Hype

Verdict: Moderate. The link is real and repeated: people with depression have higher average inflammation markers (107 studies, more than 10,000 people), experimental inflammation lowers mood in healthy adults, and cytokine treatments can trigger depression. But not every depressed person is inflamed, an anti-TNF drug did not treat depression overall, and depression has many causes, including genes, stress, and life events. "Inflammation can contribute to depression in some people" is Moderate; "inflammation causes depression" as a blanket rule overstates it. **What would change the grade:** Large randomized trials showing that lowering inflammation reliably improves depression in people chosen for high inflammation would move it toward Strong. Repeated failures in such trials would move it down.

4.12 Loops: How Inflammation, Sleep, Stress, and Mood Feed Each Other

So far we've followed a one-way street: gut inflammation sends cytokines to the brain, and the brain produces sickness behavior. Real life has loops.

Think of a microphone placed too close to a speaker. A small sound goes into the microphone, comes out louder from the speaker, goes back into the microphone, and comes out louder still, until you hear a painful squeal. That is a reinforcing feedback loop: the output feeds back into the input. Several links in the gut-brain story can work this way.

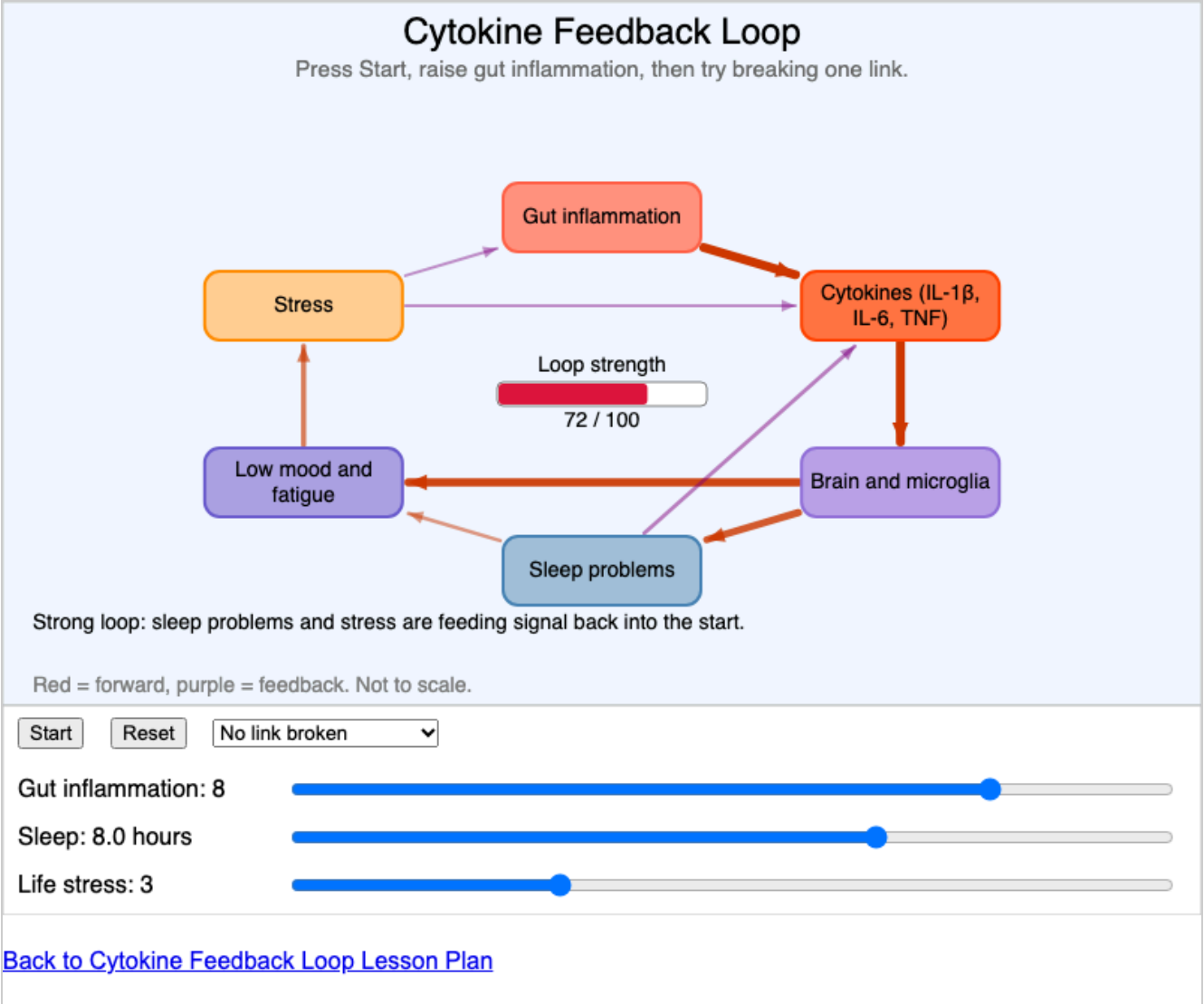
- **Inflammation disturbs sleep.** Dantzer's review notes that sleep during illness is often fragmented. In the 2022 IBD meta-analysis, sleep disturbance was one of the factors most often linked to fatigue.
- **Poor sleep goes with more inflammation.** A 2016 meta-analysis by Irwin, Olmstead, and Carroll combined 72 studies with more than 50,000 adults. Sleep disturbance was linked to slightly higher CRP and IL-6. The links were small, they were mostly correlations, and short experiments that deprived people of sleep did not consistently raise these markers, so cause is uncertain.
- **Stress raises some cytokines.** A 2007 meta-analysis by Steptoe, Hamer, and Chida combined 30 laboratory studies in which people did stressful tasks, like public speaking. Blood levels of IL-6 and IL-1β went up afterward. Chapter 7 covers stress and the gut in depth.
- **Stress may go with gut flares.** In a year-long study of 704 people with IBD in Manitoba, Canada, high perceived stress was linked to a higher chance of a symptom flare over the next few months, an association measured by questionnaire that doesn't prove stress raises gut inflammation (Bernstein and colleagues, 2010; Chapter 7 looks at this study closely).

- **Low mood and fatigue can feed stress,** by making it harder to keep up with school and friends.

Put these together and you get a loop: gut inflammation raises cytokines, cytokines worsen sleep and mood, and poor sleep and stress may push inflammation a little higher.

A loop also has more than one place where it can be broken. Treating gut inflammation is the biggest lever for someone like Riya, but better sleep or stress management might also loosen the loop, which is part of why care teams look at the whole person. The simulation below lets you play with a simplified version.

Diagram: Cytokine Feedback Loop



Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch04-cytokine-feedback-loop/main.html

Open the Cytokine Feedback Loop fullscreen

MicroSim specification: Cytokine Feedback Loop

Type: microsim **sim-id:** ch04-cytokine-feedback-loop
Library: p5.js
Status: Implemented
Bloom Level: Understand (with Analyze)
Bloom Verb: explain
Learning Objective: The learner will explain immune-to-brain signaling as a feedback loop (gut inflammation, cytokines, brain and microglia, sleep, mood, and stress) and analyze how breaking one link weakens the whole loop.

Canvas: 470 px drawing area plus 140 px controls (iframe 612 px); responsive down to about 320 px wide.

Controls: Start/Pause, Reset; link menu (no link broken; treat gut inflammation; protect sleep; manage stress); Gut inflammation slider (0 to 10, default 2); Sleep slider (4 to 10 hours, default 8); Life stress slider (0 to 10, default 3).

Rules: Six nodes on a ring (gut inflammation, cytokines, brain and microglia, sleep problems, low mood and fatigue, stress), each with a level from 0 to 1. Each frame, every node moves 3% of the way toward its slider input plus the weighted levels of the nodes that feed it (forward weights 0.25 to 0.8; feedback weights from sleep problems and stress 0.2 to 0.3; stress feeds back to both cytokines and gut inflammation). Sleep input rises as hours fall below 9. Loop strength = average of the cytokine, brain, sleep, and mood levels x 100. "Treat gut inflammation" cuts the gut input to 30%; "Protect sleep" and "Manage stress" shrink that node's input and cut its outgoing arrows to 15%.

Feedback: A status line says whether the loop is quiet (under 25), building (25 to 55), or strong (over 55), and what the chosen link-break did. Red arrows are forward signals; purple arrows are feedback.

Provenance: Routes and sickness behavior from Dantzer 2008 and Quan and Banks 2007; sleep link from Irwin 2016; stress-to-cytokine link from Steptoe 2007; stress-to-gut link from Bernstein 2010 (an association with symptom flares). All weights and numbers are illustrative teaching values.

Press **Start** with the default settings and watch the arrows. Then drag **Gut inflammation** up to 8, as in a flare. The cytokine node brightens first, then the brain, then sleep and mood, and the loop meter climbs. Now drop **Sleep** to 5 hours and raise **Life stress**: notice that the loop gets stronger even though you didn't touch the gut slider again, because the feedback arrows push extra signal back into the start of the loop.

Finally, try the link menu (it starts on **No link broken**). Treating gut inflammation drops the loop the most, but protecting sleep or managing stress also shrinks it. Ask yourself: why does breaking any single link weaken the whole loop? And why might a person feel better after treatment, but not all the way better, if stress and sleep are still pushing on the loop?

What this model leaves out

- The six boxes stand for huge, messy systems; real immune signaling involves dozens of cytokines, many cell types, and hormones like cortisol.
- All weights and numbers are made-up teaching values. The real sleep-inflammation and stress-inflammation links are small and partly uncertain in human studies.
- The model treats every person the same. In reality genes, medicines, diet, age, and life circumstances change how strong each link is.
- It shows only reinforcing feedback; the body also has calming loops, such as regulatory T cells and the vagus nerve's inflammatory reflex.
- Low mood in a chronic illness also comes from pain, worry, missed activities, and stigma, not only from cytokines.

At the Bedside: Two Kinds of Tired

Meet the patient (fictional)

Maya is 15 and a sophomore. In January she wakes up with a fever of 102°F, a sore throat, body aches, and a cough. By day two she is sleeping most of the day, barely eating, ignoring texts from friends, and crying over small things. Her dad, who knows Riya's family, asks the doctor, "Is it normal for the flu to make her this down?"

What the doctor checks: Maya's pediatrician asks when the symptoms started, who else at school has been sick, and whether she can keep fluids down. The exam checks her temperature, breathing, throat, and signs of dehydration. A quick nasal swab test confirms influenza.

Connecting the signals: The flu virus infects cells in Maya's airways. Pattern recognition receptors detect the virus and trigger inflammation, and immune cells release cytokines such as IL-1β, IL-6, and TNF. Those messages reach her brain through nerves, the circumventricular organs, and the blood-brain barrier, and the brain responds with fever, sleepiness, low appetite, and low mood.

Diagnosis: Influenza with typical sickness behavior.

Why it happens: Sickness behavior is the brain's response to immune signals (Section 4.10). It is temporary because the flu is a short infection: once the virus is cleared, cytokine levels fall and the brain's response fades.

The mind-body side: The doctor reassures Maya and her dad that feeling sad, irritable, and uninterested during the flu is a well-known effect of inflammation on the brain, not a sign of weakness. The doctor also asks them to call back if the low mood is severe or continues after her other symptoms clear up, since that would need its own check.

Treatment today: For most healthy teens, care for the flu means rest, fluids, and treatment for fever and aches as advised by the doctor or pharmacist. The CDC explains that prescription antiviral medicines work best when started within two days after symptoms begin, and doctors decide who should get them, especially people at higher risk.

What's new in research: Scientists are testing whether the vagus nerve's inflammatory reflex can be used to treat inflammatory gut disease. In a 2016 pilot study by Bonaz and colleagues, 7 adults with active Crohn's disease received an implanted vagus nerve stimulator; 2 were withdrawn because their disease worsened, and 5 improved toward remission over 6 months. A larger follow-up by D'Haens and colleagues, published in 2023, implanted stimulators in 17 adults with moderate to severe Crohn's disease that biologic drugs had not controlled; in the 16 who were treated, disease activity scores and a stool marker of gut inflammation (fecal calprotectin) fell over 16 weeks. **Evidence grade: Preliminary.** Both studies were small and open-label (everyone knew they were getting the device) with no comparison group, and as of October 2026 vagus nerve stimulation is not approved for Crohn's disease.

Your turn: reason through a variation

Three weeks later, Riya has a Crohn's flare. She feels tired, has no appetite, and her mood is low, much like Maya with the flu. But her flare lasts weeks, and even after her gut symptoms improve, some tiredness hangs on. Using this chapter, explain what is similar and what is different between the two cases.

Answer: Both involve the same basic pathway: inflammation releases cytokines that signal the brain and produce sickness behavior. The difference is time and source. Maya's inflammation comes from a short virus infection that clears; Riya's comes from her own immune system overreacting in her gut, which can last longer and return. Longer immune signaling may deepen fatigue and low mood, and after the flare, other parts of the loop (poor sleep, stress, worry about the next flare, anemia) can keep fatigue going. That's why Riya should tell Dr. Alvarez about lingering tiredness, so her care team can look for causes like anemia, poor sleep, or low mood that can be treated.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: The brain is completely sealed off from the immune system.
Reality: The blood-brain barrier blocks many molecules, but immune messages still reach the brain through the vagus nerve, circumventricular organs, transport of some cytokines, and signals relayed by barrier cells. The brain also has its own immune cells, the microglia.

Myth: Inflammation is always bad.
Reality: Inflammation is how the body fights infection and heals injuries. It becomes harmful when it is too strong, in the wrong place, or doesn't switch off, as in inflammatory bowel disease.

Myth: The tiredness of illness is "all in your head" or a sign of laziness.
Reality: Sickness behavior is triggered by real immune signals acting on the brain. In a randomized experiment, a dose of endotoxin lowered mood in healthy adults within hours. The feeling is created by the brain, but it is caused by the body.

Myth: Boosting your immune system is always a good thing.
Reality: The immune system works best when it is balanced. In conditions like Crohn's disease, it is already too active, and treatment often calms it down. Regulatory T cells exist precisely to keep immune responses in check.

Myth: 70% of your immune system is in your gut.
Reality: The gut holds about 70% of the body's antibody-making plasma cells, but only about 3% of all immune cells, according to a careful 2023 count.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Since 70% of your immune system lives in your gut, this probiotic will supercharge your immunity!"

Grade: Hype. The starting fact is wrong: the 2023 count by Sender and colleagues found only about 3% of all immune cells in the gut, though about 70% of antibody-making plasma cells are there. "Supercharging" immunity also isn't automatically good, since an overactive immune system causes problems like inflammatory bowel disease. And the post sells a product without showing any trial evidence for it. A careful version would say: "The gut is home to most of your antibody-making plasma cells and is an important immune site."

2. Predict: Sam has a stomach virus with fever and vomiting. He also has a big chemistry test in three days. Predict how his mood and focus might change during the illness, and through which pathway.

Sam will probably feel tired, unmotivated, and low, and have trouble concentrating while he is sick. The virus triggers inflammation in his gut, and cytokines such as IL-1β, IL-6, and TNF signal his brain through the vagus nerve and the blood, producing sickness behavior. Since his test anxiety already affects his gut, the stress of the upcoming test might add to the loop. Once the infection clears, the sickness behavior should fade, so asking the teacher about a makeup test would be reasonable.

3. Explain: Why do scientists call the circumventricular organs 'windows' between the blood and the brain?

Circumventricular organs are small brain areas around the ventricles that lack a complete blood-brain barrier. Molecules in the blood, including signals of inflammation and microbe patterns, can reach brain tissue there directly. Immune-like cells in these areas can respond by making cytokines that spread into nearby brain tissue, so they act like windows where the brain can sense what is happening in the blood.

4. Apply: A 17-year-old with ulcerative colitis says, 'My gut is calm now, so why am I still exhausted? I must be lazy.' Using the feedback loop and the fatigue data in this chapter, what would you tell them?

Fatigue is common even in remission: in the 2022 meta-analysis, about 47% of adults with IBD in remission reported it. Other parts of the loop, such as poor sleep, stress, low mood, and anemia, can keep fatigue going after inflammation settles. That doesn't mean laziness. The best step is to tell their care team, who can check for treatable causes like anemia, sleep problems, or depression.

5. Read the data. In the 2013 infliximab trial (Raison et al., *JAMA Psychiatry*), researchers looked at people who started with high inflammation (CRP above 5 mg/L) and counted how many had at least a 50% drop in depression scores at any point during treatment:

Group (high CRP only)	People	Responded	Response rate
Infliximab	13	8	62%
Placebo	9	3	33%

5. What does this data show, and what can't it show?

It shows a hint that blocking TNF might help depression in people with high inflammation, since the response rate was almost twice as high with infliximab. But it can't prove that, because only 22 people were in this subgroup, the difference could easily be chance (the authors report it wasn't statistically significant), and this was an exploratory subgroup analysis, while the trial's main result found no overall benefit. It also can't tell us about teens, since everyone was an adult. A helpful follow-up would be a larger trial that enrolls only people with high CRP from the start and compares infliximab with placebo.

Exercises

Remember

1. Name the three parts of the gut's barrier described in Section 4.4, from the gut contents inward.

Answer

The mucus layer, the intestinal epithelium (the one-cell-thick lining), and the tight junctions that seal the gaps between lining cells. Immune cells wait just beneath.

1. List the three pro-inflammatory cytokines that this chapter links to sickness behavior.

Answer

Interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor (TNF).

Understand

1. Explain the difference between innate and adaptive immunity, using the airport security comparison.

Answer

Innate immunity is like the generalist officers who react fast to anything suspicious using broad patterns, with no memory. Adaptive immunity is like specialists trained for one specific threat: slower the first time, very precise, and able to remember the threat so they respond faster next time.

1. In your own words, explain why Benjamin Hart described sickness behavior as a strategy rather than a weakness.

Answer

Hart argued that the changes of sickness, like resting, eating less, and pulling back from activities, are not a breakdown but organized, evolved behaviors that help fever fight infection. So the behavior is like choosing to pull over, not just running out of fuel.

Apply

1. A wellness influencer says, "Your brain is protected by the blood-brain barrier, so gut inflammation can't affect your mood." Use the four routes of immune-to-brain signaling to explain what is wrong with this argument, and give it a Hype Meter grade.
2. Using the MicroSim, set gut inflammation to 8 and record the loop strength with each option in the link menu. Rank the options from biggest to smallest effect, then explain what the ranking means and why the

model's numbers can't be used to choose a real treatment.

Analyze

1. Compare the 2010 endotoxin study and the 2020 Osimo meta-analysis. For each, answer at least three of the six questions. Which is better at showing cause, and which tells you more about everyday people with depression?
2. Riya feels exhausted during a flare and partly exhausted after it. Analyze the cytokine feedback loop to identify at least three different links that could be keeping her tired after the flare, and for each, suggest what kind of information her care team might want.

Evaluate

1. A headline reads: "Arthritis drug cures depression!" based on the 2013 infliximab trial. Evaluate the headline using the claim-box in Section 4.11 and write a more accurate one-sentence headline.
2. Should this textbook keep calling the immune system a "sense organ"? Write a paragraph weighing how the metaphor helps and how it might mislead, using at least two pieces of evidence from this chapter.

Create

1. Design a study to test whether improving sleep reduces inflammation markers in teens with IBD in remission. Describe your groups, how you would assign people, what you would measure, how long it would last, and what result would support your hypothesis.
2. Create a short explainer (under 150 words) that a teen with Crohn's disease could share with friends to explain why inflammation can make them tired and low, without blaming themselves and without exaggerating the science.

Key Takeaways

- The immune system acts like a sense organ: it samples microbes and danger signals at the body's borders and reports to the brain. Innate immunity is fast and general; adaptive immunity is slower, specific, and has memory.
- The gut's barrier has three parts: a mucus layer, a one-cell-thick intestinal epithelium, and adjustable tight junctions. Gut-associated lymphoid tissue, including Peyer's patches, samples what you swallow.
- The gut holds about 70% of the body's antibody-making plasma cells, but only about 3% of all immune cells. The "70% of your immune system" claim is Hype.
- Pattern recognition receptors trigger inflammation, a protective response that is harmful when it doesn't switch off. Regulatory T cells act as brakes.

- Cytokines such as IL-1β, IL-6, and TNF reach the brain through nerves (especially the vagus), circumventricular organs, transport across the blood-brain barrier, and relays from barrier cells. Microglia, the brain's own immune cells, respond.
- Sickness behavior (tiredness, low appetite, withdrawal, low mood) is a real, brain-driven response to inflammation, shown experimentally in humans. Fatigue is common in IBD, even in remission.
- Inflammation can contribute to depression in some people (Moderate), but it is not the cause of all depression, and feedback loops with sleep and stress mean there is more than one place to intervene.

You decoded the immune system's messages!



You can now trace a cytokine from an inflamed gut all the way to a tired, low feeling in the brain, and you know why "70%" deserves a skeptical look. Next, in Chapter 5, we'll take on the most famous gut-brain number of all: the claim that 90% of your serotonin is made in your gut.

Quiz: The Immune System as a Sense Organ

Test your understanding of Chapter 4. Choose the best answer, then click **Show Answer** to check.

Question 1

Which statement best describes innate immunity?

A. A slow, highly specific response that remembers each invader it has met

B. A fast, general response that recognizes broad patterns shared by many microbes

C. A response made only by antibody-producing plasma cells in the gut

D. A response that begins only after the brain sends a signal down the vagus nerve

Show Answer

The correct answer is **B**. Innate immunity responds within minutes to hours to broad patterns, such as pieces of bacterial walls, and has no memory. Option A describes adaptive immunity, which is slower the first time but specific and able to remember.

Concept Tested: Innate Immunity **Bloom's Level:** Remember

Question 2

According to the 2023 count by Sender and colleagues, what share of the body's immune cells are in the gut?

A. About 70% of all immune cells

B. About 50% of all immune cells

C. About 20% of all immune cells

D. About 3% of all immune cells, though about 70% of antibody-making plasma cells

Show Answer

The correct answer is **D**. The careful 2023 count found about 3% of all immune cells (and about 5% of lymphocytes) in the gut. The popular "70%" figure matches the gut's share of antibody-making plasma cells, not of the whole immune system, so option A mixes up the two.

Concept Tested: Gut-Associated Lymphoid Tissue **Bloom's Level:** Remember

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Question 3

What is a circumventricular organ?

A. A small brain area near the ventricles that lacks a complete blood-brain barrier

B. A cluster of immune cells in the small intestine that samples food

C. A nerve that carries signals from the gut to the brainstem

D. A layer of mucus that keeps bacteria away from the gut lining

Show Answer

The correct answer is **A**. Circumventricular organs sit around the brain's fluid-filled ventricles and lack a full blood-brain barrier, so blood-borne signals can reach brain tissue there. Option B describes a Peyer's patch, part of gut-associated lymphoid tissue, which is a different kind of sampling station.

Concept Tested: Circumventricular Organ **Bloom's Level:** Remember

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Question 4

Why does the chapter describe sickness behavior as an evolved strategy rather than simple weakness?

A. Because sick people always feel better if they keep exercising

B. Because sickness behavior is caused by bacteria controlling the brain directly

C. Because resting, eating less, and withdrawing are organized behaviors that help fever fight infection

D. Because sickness behavior only happens in animals, never in humans

Show Answer

The correct answer is **C**. Benjamin Hart proposed in 1988 that sickness behavior is an organized, evolved response that helps fever fight viral and bacterial infections, not simply a breakdown. Option D is wrong because a 2010 randomized experiment showed that inflammation lowers mood in healthy humans too.

Concept Tested: Sickness Behavior **Bloom's Level:** Understand

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Question 5

How do tight junctions contribute to the gut's barrier?

A. They make antibodies that coat bacteria in the gut

B. They seal the gaps between neighboring lining cells and control what slips between them

C. They form a thick wall of muscle that pushes bacteria out of the gut

D. They completely block water and every molecule from passing between cells

Show Answer

The correct answer is **B**. Tight junctions are protein seals that link neighboring epithelial cells, like mortar between stones. Option D overstates it: the seal is adjustable and lets water and some small molecules through, which is why "leaky gut" claims need careful checking in Chapter 6.

Concept Tested: Tight Junction **Bloom's Level:** Understand

Question 6

Which description best explains how gut cytokines can reach the brain even though the brain has a blood-brain barrier?

A. Cytokines dissolve the blood-brain barrier completely during every infection.

B. Cytokines cannot affect the brain; sickness feelings come only from the gut.

C. Only bacteria, not cytokines, can send signals to the brain.

D. Cytokines activate vagus nerve fibers, act at circumventricular organs, are carried across in some cases, and trigger barrier cells to relay signals.

Show Answer

The correct answer is **D**. Quan and Banks described four routes: the nerve route (especially the vagus), circumventricular organs, transport of some cytokines across the barrier, and signals relayed by barrier cells. Option B reflects the misconception that the brain is sealed off from the immune system.

Concept Tested: Immune-to-Brain Signaling **Bloom's Level:** Understand

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Question 7

A 16-year-old has a stomach virus with fever. She sleeps most of the day, has no appetite, and doesn't want to talk to friends. Her brother says she is just being lazy. Which response best applies this chapter?

A. Her immune cells are releasing cytokines that signal her brain, producing sickness behavior that should fade as the infection clears.

B. Her symptoms prove she has depression, which inflammation always causes.

C. Her gut bacteria are making her choose to stay in bed.

D. Her symptoms mean her immune system is too weak and needs boosting.

Show Answer

The correct answer is **A**. Infection triggers inflammation, and cytokines such as IL-1β, IL-6, and TNF act on the brain to cause tiredness, low appetite, and withdrawal. This is temporary and expected. Option B overstates the evidence: inflammation can contribute to depression in some people, but short sickness behavior is not a depression diagnosis.

Concept Tested: Sickness Behavior **Bloom's Level:** Apply

Question 8

In the Cytokine Feedback Loop MicroSim, a student sets gut inflammation to 0 but sets sleep to 5 hours and stress to 8. The loop is still active. Which change would most likely weaken it most?

A. Treating gut inflammation, because that always helps most

B. Raising stress further, to push the loop past its limit

C. Protecting sleep or managing stress, because those feedback arrows are now driving the loop

D. Nothing, because loops can never be broken once they start

Show Answer

The correct answer is **C**. With gut inflammation already at 0, there's little left to treat at the gut; the signal is coming from sleep problems and stress feeding back into cytokines (and, for stress, into gut inflammation). Breaking those links weakens the loop. Option A is a common assumption, but which link matters most depends on where the signal is coming from.

Concept Tested: Cytokine **Bloom's Level:** Apply

Question 9

In the 2013 infliximab trial for depression, infliximab did not beat placebo overall, but people with high CRP seemed to respond better. What is the most reasonable conclusion?

A. Anti-TNF drugs cure depression and should be used for everyone with depression.

B. Inflammation plays no role in depression at all.

C. The trial proves high CRP causes depression.

D. Blocking TNF may help a subset of people with high inflammation, but a larger trial designed for that group is needed.

Show Answer

The correct answer is **D**. The main result was no overall benefit, and the high-CRP finding came from a small, exploratory subgroup (22 people) that could reflect chance. Option B goes too far the other way: other human evidence, such as experimental endotoxin and interferon studies, supports a contributing role for inflammation in some people.

Concept Tested: Tumor Necrosis Factor **Bloom's Level:** Analyze

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Question 10

Germ-free mice have immature microglia, and microbial short-chain fatty acids help restore them (Erny et al., 2015). Why does this chapter grade "Your gut bacteria control your brain's immune cells" as Preliminary?

A. The results come from mice raised with no microbes at all, and human evidence is missing.

B. The study was done in thousands of people but had no control group.

C. The study showed that microglia are made in the bone marrow, not the brain.

D. Microglia are not immune cells, so the study was measuring the wrong thing.

Show Answer

The correct answer is **A**. Germ-free mice are an extreme situation no person lives in, and no human study has shown that normal microbe differences change microglia in a meaningful way. Option C is wrong: fate-mapping studies in mice showed that microglia come from early embryonic precursors and maintain themselves in the brain.

Concept Tested: Microglia **Bloom's Level:** Analyze

Chapter 5: Chemical Messengers and the Serotonin Myth

Summary

"Ninety percent of your serotonin is in your gut" is one of the most shared gut-brain facts online, and it's true. The conclusion people draw from it, that your gut controls your happiness, is not. This chapter explains how nerve cells pass chemical messages, follows serotonin from the amino acid tryptophan to the cells that make it, and shows why serotonin made in the gut stays out of the brain. It covers how SSRI medicines work and why they often upset the stomach at first, what the "low serotonin causes depression" debate is really about, and what we know (and don't) about chemicals like GABA and dopamine made by gut microbes.

Concepts Covered

1. Synapse
2. Neurotransmitter
3. Serotonin
4. Tryptophan
5. Tryptophan Hydroxylase
6. Enterochromaffin Cell
7. Serotonin Transporter
8. SSRI
9. Blood-Brain Barrier
10. Gut Serotonin Mood Myth
11. Dopamine
12. GABA
13. Acetylcholine
14. Microbe-Made Neurotransmitter
15. Kynurenine Pathway
16. Spore-Forming Bacteria

Prerequisites

- Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading) for enteric neurons and the Hype Meter
- Chapter 2: The Vagus Highway for enteroendocrine cells and upward vagus signals
- Chapter 3: Meet the Microbiome for germ-free mice and correlation vs causation
- Chapter 4: The Immune System as a Sense Organ for inflammation and the inflammation-depression debate

The most famous gut-brain number



If you've seen one gut-brain fact on social media, it's probably "90% of your serotonin is made in your gut." That true number is often used to sell a false conclusion. Learning exactly where serotonin goes will help you spot a whole family of wellness myths. It also explains something many teens on antidepressants notice: why a brain medicine can upset your stomach.

5.1 Sam's Cousin Has a Theory

Sam's older cousin posted a video that got thousands of likes. Over a shot of a smoothie, the caption read: "90% of your serotonin is made in your GUT. Serotonin = happiness. So heal your gut and you'll be happy. Link in bio for my gut-healing powder." Sam, who has IBS and gets stomach trouble before big races, sent it to Riya with one word: "Real?" (Sam and Riya are fictional students who appear throughout this book.)

Riya thought about it. The first sentence sounded familiar, and she had heard Dr. Alvarez mention gut serotonin once. But the jump from "made in your gut" to "you'll be happy" felt too easy. This chapter explains why: the first sentence is solid science, the second is an oversimplification, and the third does not follow from the first two at all. To see why, we need to know what serotonin is, where it's made, and where it can and can't go.

5.2 Two Bakeries, One Recipe

Start with a comparison. Picture two towns separated by a high wall with a few guarded gates. Each town has its own bakery, and by coincidence both bake the same kind of bread from the same flour. The bakery in the big valley town makes far more bread, and that bread feeds the valley. The bakery in the hilltop town is smaller, but it makes all of the bread the hilltop eats. The guards won't let finished bread through the gates, but they will let sacks of flour through.

Now suppose someone says, "90% of all the bread in this region is baked in the valley, so if you want the hilltop to eat better, improve the valley bakery." You can see the problem. The valley's bread never reaches the hilltop. The only thing that crosses the wall is flour.

In your body, the valley is your gut, the hilltop is your brain, the wall is the blood-brain barrier, the bread is serotonin, and the flour is an amino acid called tryptophan. Keep this picture in mind. The rest of the chapter fills in the details.

5.3 How Nerve Cells Pass Chemical Messages

Here's a quick refresher from biology. A neuron sends an electrical signal down its long fiber (axon) to its tip. But neurons don't usually touch the next cell. There's a tiny gap, and the signal has to cross it as chemistry.

A **synapse** is the junction where a neuron passes a signal to another cell (another neuron, a muscle cell, or a gland cell), usually across a tiny gap called the synaptic cleft. A **neurotransmitter** is a chemical messenger that a neuron releases at a synapse; it crosses the gap and binds to receptor proteins on the receiving cell, making that cell more or less likely to fire or changing how it works. After the message is delivered, the neurotransmitter is cleared away, often by being pumped back into the cell that released it, so the next message can be sent cleanly. For a deeper review, see From Neuron to Bedside, Chapter 3.

One more idea matters here. The same chemical can act as a neurotransmitter when a neuron releases it into a synapse and as a hormone when a cell releases it into the blood to act far away. Serotonin does both, and that is exactly why it causes so much confusion.

Four neurotransmitters show up again and again in gut-brain research:

Serotonin (also called 5-hydroxytryptamine, or 5-HT) is a chemical messenger made from the amino acid tryptophan. In the brain it acts as a neurotransmitter involved in mood, sleep, appetite, and many other functions; in the gut it controls movement, secretion, and sensations like nausea; and in the blood it is carried by platelets.

Dopamine is a neurotransmitter that the brain uses in movement, motivation, and learning from rewards; it also acts in other parts of the body, including the gut.

GABA (gamma-aminobutyric acid) is the brain's main inhibitory neurotransmitter, meaning it mostly makes receiving neurons less likely to fire, like a brake pedal.

Acetylcholine is a neurotransmitter that activates muscles and many glands; in the gut it is a main "go" signal used by enteric motor neurons to make smooth muscle contract, and it is the main chemical the vagus nerve's outgoing (motor) fibers release onto their targets. (You met it in Chapter 1 as the messenger of excitatory enteric motor neurons.)

Messenger	A main brain role	A main gut role	Made by gut microbes?
Serotonin	Mood, sleep, appetite	Movement, secretion, nausea signals	Microbes influence how much the gut makes (mouse studies)

Messenger	A main brain role	A main gut role	Made by gut microbes?
Dopamine	Movement, motivation, reward	Local control of gut function	Microbes take part in dopamine chemistry (mostly lab and animal studies)
GABA	Main "brake" signal	Local signaling in the gut wall	Some common gut bacteria make large amounts in the lab
Acetylcholine	Attention, memory	Main "go" signal for gut muscle	Not a focus of this chapter

5.4 Meet Serotonin: More Than a "Happy Chemical"

Serotonin's story starts in the gut. Vittorio Erspamer studied a substance made by special hormone cells in the gut lining and called it "enteramine." In 1952, Erspamer and Asero reported in the journal *Nature* that enteramine was the same molecule as 5-hydroxytryptamine, the chemical we now call serotonin.

So serotonin has been a gut chemical from the start. Reviews by Michael Gershon (2013) and by Gary Mawe and Jill Hoffman (2013) describe its jobs outside the brain:

- **In the gut wall,** serotonin released from the lining activates sensory nerve endings that start local reflexes for movement and secretion, and that send information to the brain through the vagus and spinal nerves.
- **In sensations,** activation of those vagus and spinal fibers can lead to nausea, vomiting, fullness, and discomfort.
- **In the blood,** platelets (cell fragments that help blood clot) soak up serotonin and store it, which helps with clotting.
- **In bone,** gut-made serotonin acting as a hormone slows the growth of bone-building cells, at least in animal studies.

Inside the brain, serotonin is made mainly by neurons in the brainstem, whose fibers reach many other brain areas. Brain serotonin is involved in mood, but also in sleep, appetite, pain, and much more. Calling it "the happy chemical" is a bit like calling a smartphone "a calculator": not wrong, but it misses most of what it does.

Two names, one molecule



When you read research, watch for "5-HT." It's just the chemical name for serotonin (5-hydroxytryptamine), and it's the same molecule whether it's in your gut, your blood, or your brainstem. What differs is where it's made and where it can travel.

5.5 How Serotonin Is Made: Tryptophan and Its Enzymes

Every bit of serotonin in your body starts as tryptophan.

Tryptophan is an essential amino acid, meaning your body can't make it and must get it from protein in food, such as meat, dairy, seeds, and many other foods. A 2016 review by Jenkins and colleagues describes it as found in many protein-based foods. Besides being a building block for proteins, tryptophan is the raw material for serotonin.

To turn tryptophan into serotonin, cells need an enzyme (a protein that speeds up a chemical reaction). **Tryptophan hydroxylase** (TPH) is the enzyme that performs the first and key step in making serotonin from tryptophan. There are two versions.

- **TPH1** works in the gut's serotonin-making lining cells and other cells outside the brain.
- **TPH2** works in neurons, including the brain's serotonin neurons and serotonin-making neurons in the gut wall.

The second version was discovered in 2003 by Diego Walther and colleagues, who reported it in *Science*. Two separate enzymes in two separate places means two separate supplies of serotonin, like the two bakeries using different ovens. Drug designers have used this: a 2013 review by Mawe and Hoffman describes TPH inhibitors designed to lower gut serotonin without reaching the brain, by limiting their ability to cross the blood-brain barrier.

The recipe has two steps. Tryptophan hydroxylase turns tryptophan into an in-between molecule called 5-HTP (5-hydroxytryptophan), and a second enzyme then turns 5-HTP into serotonin (Jenkins 2016). Unlike serotonin, 5-HTP can be carried across the blood-brain barrier (Section 5.7), and it is sold in some dietary supplements.

A 2020 review by Maffei notes that too much 5-HTP can cause serotonin syndrome, a dangerous overload of serotonin activity, and MedlinePlus lists tryptophan among the products that can interact with fluoxetine, an SSRI you'll meet in Section 5.9. Dietary supplements are not approved as drugs to treat any condition, so questions about them belong with a doctor.

Most tryptophan takes a different road

Serotonin gets the headlines, but it uses only a small share of the tryptophan you eat. The **kynurenine pathway** is the main chemical route for breaking down tryptophan, mostly in the liver, producing a molecule called kynurenine and a series of other products, some of which can act on brain cells. Dantzer's 2008 review (the same one from Chapter 4) states that more than 95% of dietary tryptophan is broken down through the kynurenine pathway, and only a small portion becomes serotonin.

This pathway links back to Chapter 4. Dantzer's review describes how some pro-inflammatory cytokines boost an enzyme (called IDO) that pushes tryptophan toward kynurenine. In mice given a bacterial trigger for inflammation, this shift happened alongside depression-like behavior, and some kynurenine products can act on receptors in the brain. Whether this matters for human depression is still being studied, so treat it as a mouse-based idea, not a settled explanation. A 2018 review by Agus, Planchais, and Sokol adds that gut

microbes directly or indirectly influence how tryptophan is split among serotonin, kynurenine, and a third route that makes molecules called indoles.

5.6 The Gut's Serotonin Factories: Enterochromaffin Cells

In Chapter 2 you met enteroendocrine cells, the hormone-releasing sensor cells scattered through the gut lining. One type does most of the body's serotonin work.

An **enterochromaffin cell** (EC cell) is a type of enteroendocrine cell in the gut lining that senses conditions inside the gut and releases serotonin, making most of the body's serotonin using the enzyme TPH1. Here is the fact this book uses throughout:

> More than 90% of the body's serotonin is made in the gut, mostly by enterochromaffin cells (some estimates say about 95%).

A 2015 study by Yano and colleagues and a 2017 study by Bellono and colleagues both put it at more than 90%; Gershon's 2013 review puts about 95% of the body's serotonin in the gut. Surprisingly few cells do this work. Bellono's team reported that EC cells make up less than 1% of the cells lining the intestine. Working with lab-grown mouse gut tissue (organoids) and mice, they also showed that EC cells carry specific chemical-sensing receptors, are electrically excitable, and form synapse-like connections with sensory nerve fibers. That makes them tiny chemical sensors wired to the nervous system, a good example of the "gut as sense organ" idea from Chapter 4.

What happens to gut serotonin after an EC cell releases it? Mawe and Hoffman's review traces three paths, and they are the same three you'll see in the MicroSim:

1. **It acts on nearby nerves.** Serotonin binds receptors on the endings of enteric, vagal, and spinal sensory nerves, starting local reflexes and sending signals toward the brain. Note the key difference: the *nerve signal* travels to the brain; the serotonin molecule does not.
2. **It is cleared back into lining cells.** The message has to be switched off, and here a pump does the work.
3. **It enters the blood and is stored in platelets.** Serotonin not taken up by the lining enters tiny blood vessels, where platelets take it in and store it.

The pump in path 2 is worth its own definition. The **serotonin transporter** (SERT) is a protein pump in cell membranes that moves serotonin from outside a cell back inside, ending its signal. In the brain, SERT sits on serotonin neurons and recycles serotonin from synapses. In the gut, Mawe and Hoffman report that SERT is found on essentially all of the lining's epithelial cells, which clear away serotonin after EC cells release it. Platelets use SERT too, which is how they load up on serotonin from the blood.

If you're going through this

If you have IBS like Sam, you may hear that serotonin is involved in gut sensitivity and bowel habits. That's an active research area, and some IBS medicines do act on gut serotonin receptors, which your care team can explain. What it doesn't mean is that your symptoms are "all chemical" or that a supplement can rebalance them. If a product promises to "fix your serotonin," bring it to your doctor before you try it.

5.7 The Wall Between: The Blood-Brain Barrier

Now for the wall in our two-towns picture.

The **blood-brain barrier** (BBB) is the specialized lining of the brain's blood vessels, made of tightly sealed endothelial cells supported by other cells, that tightly controls which ions, molecules, and cells can pass from the blood into the brain. A 2015 review by Daneman and Prat describes how these vessel cells regulate traffic between blood and brain far more strictly than vessels elsewhere in the body. Think of it as the wall with a few guarded gates: specific transporter proteins act as gates that let in nutrients the brain needs, such as certain amino acids.

Here is the fact at the heart of this chapter:

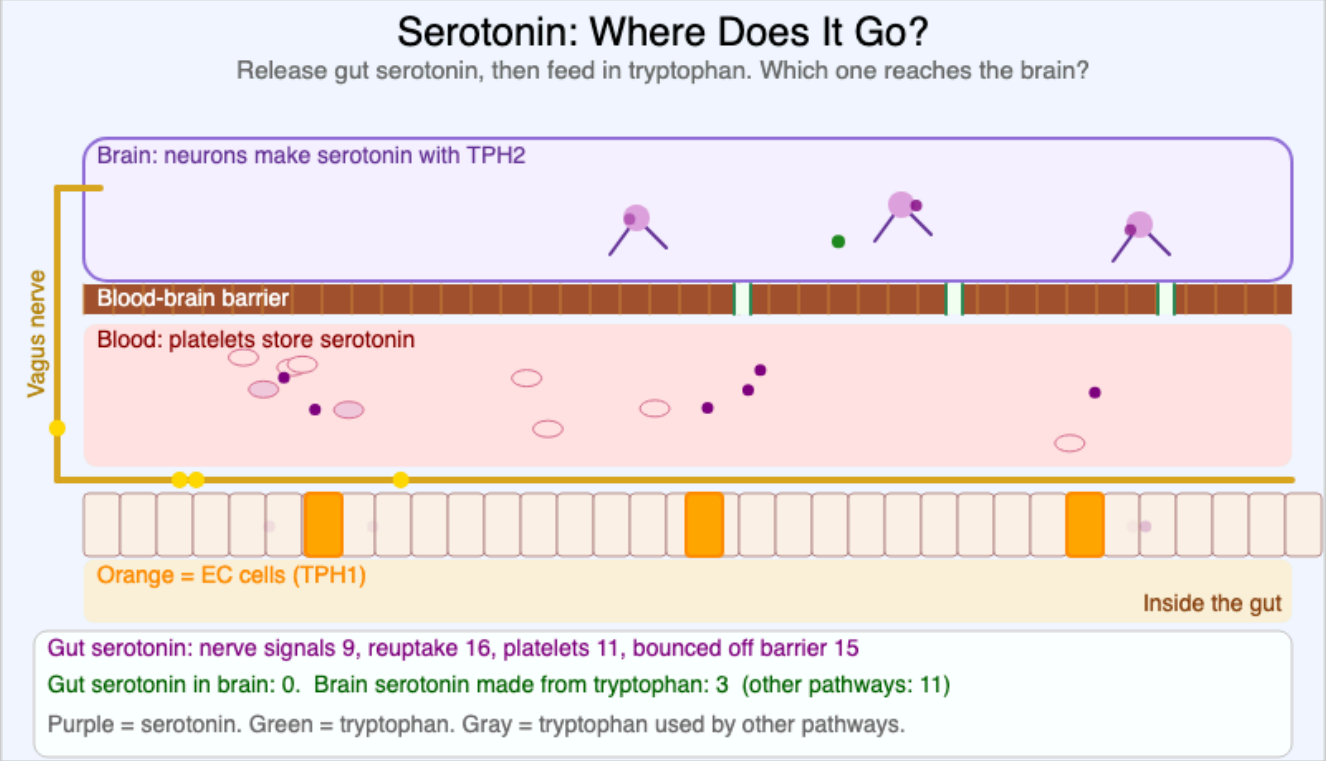
> Serotonin made in the gut does not cross the blood-brain barrier. The brain makes its own serotonin from tryptophan, an amino acid that can cross.

A 2020 editorial by Bektaş and colleagues, titled "Does serotonin in the intestines make you happy?", states this directly: serotonin made in the intestines cannot reach the brain because it can't cross the blood-brain barrier, so the gut's serotonin acts as a peripheral hormone and isn't what sets emotional state. A 2022 review by Cai and colleagues likewise describes the body's serotonin and the brain's serotonin as functionally separate systems for this reason. A 2025 review of nutrition and the serotonin system in *Advances in Nutrition* (Tang and colleagues) says the same: serotonin made in the body stays out of the brain, acts locally (for example, on gut movement), and can still affect the brain indirectly through the vagus nerve. Bektaş's editorial adds a related myth: eating bananas, which contain serotonin, doesn't raise brain serotonin either, for the same reason.

So how does the brain get its supply? Tryptophan crosses. The 2016 Jenkins review explains that tryptophan rides into the brain on a transporter that carries a group of "large neutral amino acids," and that it competes with those other amino acids for a seat. Once inside, brain neurons use TPH2 to turn it into serotonin. That's the flour going through the gate, with the hilltop bakery doing the baking.

One caution about barriers: in **germ-free mice**, a 2014 study by Braniste and colleagues found that the blood-brain barrier was leakier than normal and tightened after the mice received gut microbes. That's an interesting mouse result (Chapter 6 covers it), but even a somewhat leaky barrier in mice is a long way from "gut serotonin floods the human brain," and no study in this chapter shows that.

Diagram: Serotonin: Where Does It Go?



Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch05-serotonin-where/main.html

Open Serotonin: Where Does It Go? fullscreen

MicroSim specification: Serotonin: Where Does It Go?

Type: microsim **sim-id:** ch05-serotonin-where
Library: p5.js
Status: Implemented
Bloom Level: Understand
Bloom Verb: distinguish
Learning Objective: The learner will distinguish gut (peripheral) serotonin from brain (central) serotonin by tracing where serotonin released by enterochromaffin cells goes (nerves, reuptake, platelets, blocked at the blood-brain barrier) and how the brain makes its own serotonin from tryptophan.

Canvas: 460 px drawing area plus 110 px controls (iframe 572 px); responsive to about 380 px wide.

Controls: Start/Pause, Reset, "SSRI (blocks SERT)" checkbox; "Release gut serotonin" and "Eat protein (tryptophan)" buttons (each starts the animation); Show labels checkbox.

Rules: Each release sends 7 purple serotonin dots from each of 3 EC cells. Without an SSRI, about 35% act on the nerve (a gold pulse travels up the vagus nerve to the brainstem), 35% are taken back into lining cells by SERT, and 30% enter the blood, where platelets that touch them take them up. With the SSRI box checked, reuptake and platelet uptake are blocked, so about 55% act on the nerve and the rest stay in the blood longer. Serotonin dots that reach the blood-brain barrier always bounce off. Each meal adds 15 green tryptophan dots; about 75% turn gray (used by other pathways, mainly kynurenine) and about 25% pass through transporter gates into the brain, where neurons turn them into serotonin. Brain serotonin lingers longer with the SSRI box checked.

Feedback: A counter panel tallies nerve signals, reuptake, platelet uptake, bounces off the barrier, gut serotonin in the brain (always 0), and brain serotonin made from tryptophan.

Provenance: Mawe and Hoffman 2013 (three fates of gut serotonin; SERT on epithelial cells and platelets); Bektaş 2020 and Cai 2022 (no BBB crossing); Jenkins 2016 (tryptophan transport); Dantzer 2008 (most tryptophan to kynurenine). Percentages and speeds are illustrative.

Press **Release gut serotonin** and follow the purple dots. Some hit the gold nerve line under the lining, and a pulse travels up the vagus nerve: that's information reaching the brain, not serotonin. Some disappear into the lining cells (reuptake by SERT), and some drift into the blood, where platelets turn purple as they store them. Watch the dots that reach the blood-brain barrier: the counter for "gut serotonin in brain" never moves off zero, however many times you press the button.

Now press **Eat protein (tryptophan)**. Most green dots turn gray and fade (used by the kynurenine pathway and other routes), but a few find the gates in the barrier, cross, and turn purple inside the brain's neurons. Finally, check **SSRI (blocks SERT)** and release more gut serotonin. With reuptake blocked, more serotonin reaches the gut nerves, which is one reason SSRIs can cause nausea or loose stools. Ask yourself: did the SSRI change how much gut serotonin reaches the brain?

What this model leaves out

- Real serotonin release is constant and tiny, measured in molecules, not a few dozen dots on a button press; the percentages are made-up teaching values. In real life, far more of the tryptophan you eat goes to other pathways than the sim shows (more than 95%).
- The model shows only one type of serotonin receptor on one nerve. The gut has many serotonin receptor types with different effects, including on gut muscle and the lining.
- The brain's serotonin neurons are in the brainstem and send fibers across the whole brain; the sim shows three cartoon neurons.
- The sim leaves out how the body breaks down serotonin in the blood over time, and serotonin's roles in bone and clotting.
- SSRIs take weeks to change mood and work through changes in brain circuits over time, which the sim does not show.

5.8 The Gut Serotonin Mood Myth

Now we can grade Sam's cousin's post. The **gut serotonin mood myth** is the popular but unsupported claim that because most of the body's serotonin is made in the gut, the gut directly controls mood or happiness, and so "healing your gut" will raise your brain's serotonin and make you happier.

It's a chain of three links, and only the first one holds:

Link in the claim	Verdict	Why
"More than 90% of serotonin is made in the gut"	True	Yano 2015; Bellono 2017; Gershon 2013
"Serotonin = happiness"	Oversimplified	Brain serotonin does many jobs; depression is not simply "low serotonin" (Section 5.10)
"So healing your gut makes your brain happier"	Does not follow	Gut serotonin can't cross the blood-brain barrier; the brain makes its own

Grade the chain, not the first link



I see this trick everywhere: start with a true number, then attach a conclusion that sounds like it follows. When a claim has several steps, I check each link separately, because a chain is only as strong as its weakest one.

Hype Meter: "90% of your serotonin is in your gut, so your gut controls your happiness"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. The number is Strong: more than 90% of the body's serotonin is made in the gut, mostly by enterochromaffin cells. But that serotonin does not cross the blood-brain barrier, and the brain makes its own from tryptophan using a different enzyme (TPH2). Gut serotonin mainly runs gut movement, secretion, sensations like nausea, and platelet storage. The gut does send signals to the brain through nerves and other routes, but "gut serotonin controls your mood" is not what the evidence shows. **What would change the grade:** Human studies showing that changing gut serotonin production, by itself, reliably changes brain serotonin and mood. Drugs designed to lower gut serotonin without entering the brain would be a natural way to test this.

That doesn't mean the gut has nothing to do with the brain; this whole book is about the ways it does. Gut serotonin can affect the brain *indirectly*, by activating vagus and spinal nerves that carry signals upward (Chapter 2), and the gut influences the brain through immune signals (Chapter 4) and microbial chemicals (Section 5.11 and Chapter 6). The myth isn't "the gut and brain are connected." The myth is that gut-made serotonin is the brain's happiness supply.

5.9 SSRIs: Why a Brain Medicine Can Upset Your Stomach

Some of the most widely prescribed medicines for depression and anxiety work on the serotonin transporter.

An **SSRI** (selective serotonin reuptake inhibitor) is a type of medicine that blocks the serotonin transporter, so serotonin stays outside cells longer after it is released; SSRIs such as fluoxetine are prescribed for depression, anxiety disorders, and other conditions. MedlinePlus, the US National Library of Medicine's drug information site, explains that fluoxetine is in this class and works by increasing the amount of serotonin available, and that it may take 4 to 5 weeks or longer to feel the full benefit.

An SSRI taken as a pill doesn't only reach the brain; it reaches the whole body, including the gut, where SERT is on essentially every lining cell and on platelets. Block those pumps, and gut serotonin lingers longer near the nerve endings that control gut movement and send nausea signals. Mawe and Hoffman's review notes that SSRIs can change gut movement in people, sometimes speeding it up and sometimes slowing it down.

MedlinePlus lists nausea, heartburn, and diarrhea among fluoxetine's possible side effects. That's the same two-towns story in reverse: the medicine is aimed at the hilltop, but it also changes the valley.

For teens, one more fact matters. MedlinePlus carries a warning for fluoxetine and similar medicines: they may increase the risk of suicidal thoughts and actions in children, teenagers, and young adults under 24, especially in the first few months or when the dose is increased. That's why doctors watch closely at the start and ask families to call right away about new or worse depression or thoughts of self-harm. If you ever have thoughts of suicide, you can call or text 988 in the US. MedlinePlus is also clear that people shouldn't stop taking fluoxetine without talking to their doctor, because stopping suddenly can cause withdrawal symptoms.

Sam asked his own doctor about the post. She explained that several IBS treatments act on gut serotonin receptors, which is good evidence that serotonin matters for gut symptoms. "But notice," she said, "those medicines are aimed at your gut's serotonin system, and SSRIs are aimed at your brain's, and when one affects the other's territory, we call it a side effect."

For families

If your teen starts an SSRI and gets an upset stomach in the first weeks, that's a common and usually understood side effect, not a sign the medicine is "poisoning" them or that they are weak. Help them write down what they notice and when, and bring it to the prescriber rather than stopping or changing the dose at home. Also know the warning signs the prescriber will mention, such as new or worse depression or thoughts of self-harm, and call right away if you see them.

5.10 Is Depression Just "Low Serotonin"?

For decades, ads and textbooks explained depression as a "chemical imbalance" caused by too little serotonin. Scientists have been questioning that simple story for a long time.

In July 2022, Joanna Moncrieff and colleagues at University College London published a widely discussed umbrella review (a review of reviews) in *Molecular Psychiatry*. They gathered 17 studies, including systematic reviews, meta-analyses, and large genetic studies, covering measures such as serotonin levels in body fluids, serotonin receptor and transporter imaging, tryptophan depletion experiments, and serotonin transporter genes. They concluded that there was no consistent evidence that depression is caused by lowered serotonin activity.

The review sparked strong reactions, and many comments and replies were published. In 2023, a group of 35 psychiatrists and brain scientists led by Sameer Jauhar answered in the same journal (Jauhar and colleagues, 2023). They argued that the review's conclusion was overstated. They criticized how it chose and reported studies, and they said that tryptophan depletion experiments and brain imaging do point to a role for serotonin in people who are vulnerable to or living with depression. Moncrieff's team published a reply the same year and stood by its conclusion.

New data keep arriving, too. In a 2023 brain-imaging (PET) study, Erritzoe and colleagues gave a single dose of amphetamine, a drug that makes neurons release serotonin (along with other messengers), to 17 adults in a depressive episode who were not taking antidepressants and to 20 adults without depression (Erritzoe and colleagues, 2023). The scans showed less serotonin release in the depressed group. That is one small study. It measured release during an episode, not whether low serotonin comes first, so it can't settle the cause question. The debate is still going on. Two points help you read it fairly:

- **What the review is about:** whether low serotonin is the *cause* of depression. Rejecting a simple "low serotonin" story is not the same as saying serotonin plays no role in mood.
- **What the review is not about:** whether antidepressants help. The review didn't test that, and it isn't evidence that people should stop their medicine. SSRIs could help through effects that develop over weeks, even if depression doesn't start with low serotonin.

As Bektaş and colleagues put it in their 2020 editorial, psychiatric conditions don't develop from a single cause. Depression is linked to many factors, including stress, life events, and inflammation in some people (Chapter 4). The slogan "depression is low serotonin" is too simple for the evidence.

Hype Meter: "Depression is caused by low serotonin"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. A 2022 umbrella review of 17 studies found no consistent evidence that depression is caused by lowered serotonin, and depression is widely understood to have more than one cause. Critics of that review argue that the serotonin system is disturbed in some people with depression (Jauhar 2023; Erritzoe 2023), and serotonin may be involved in how some treatments work. But even those critics describe a role for serotonin, not a single cause, so the simple cause-and-effect slogan is not supported. This grade is about the slogan only; it is not a judgment on whether antidepressants help, which is a separate question. **What would change the grade:** Consistent, repeated human evidence that serotonin activity is reduced before depression begins, and that restoring it reliably prevents or ends depression.

Don't flip the myth



A common mistake is to swing from "depression is low serotonin" to "antidepressants are fake." The 2022 review tested the first claim, not the second, so never treat it as a reason to change a medicine; that's a conversation for you and your doctor.

5.11 Do Gut Microbes Make Your Mood?

The other big claim in gut-brain posts is that your gut bacteria make "happy chemicals." Let's check the evidence, one chemical at a time.

Microbes that turn up the gut's serotonin

Spore-forming bacteria are bacteria that can survive harsh conditions by forming tough, dormant spores; in the gut, a mix of them (dominated by a group called Clostridia) has been shown in mice to boost serotonin production by the gut lining. In 2015, Jessica Yano, Elaine Hsiao, and colleagues at Caltech reported in *Cell* that germ-free mice had lower serotonin in the colon and blood than normal mice. When the researchers gave germ-free mice spore-forming bacteria taken from mouse or human gut microbes, the mice's EC cells made more serotonin, partly by raising TPH1 levels. The change also affected gut movement and how platelets worked.

This is careful work, but notice what it is and isn't. The bacteria raised *gut and blood* serotonin, the serotonin that can't enter the brain. And it was done in mice. So it supports "in mice, certain gut bacteria increase the gut's serotonin production," not "your bacteria control your brain's serotonin."

How to read a gut-brain claim: spore-forming bacteria and gut serotonin (Yano et al., 2015)

Question	This study
Mouse or human?	Mouse. Germ-free and normal mice; the bacteria came from mouse and human gut samples, but all effects were measured in mice (plus some cell cultures).
Correlation or cause?	Cause, in mice: adding spore-forming bacteria to germ-free mice raised gut and blood serotonin, an experiment rather than an observation.
How many?	Small groups, often 3 to 8 mice per group in a given experiment, which is typical for mouse work.
How long?	Short: many measurements were taken about two weeks after the bacteria were given.
Who paid for it?	Public and university funding: an NIH Director's Early Independence Award, a Caltech center award, the National Science Foundation, and grants from three NIH institutes (NHGRI, NIDDK, NIMH).
Is something being sold?	No product in the paper. But it is often cited in ads for probiotics and "serotonin-boosting" supplements, which the study never tested.

The conclusion: strong evidence, in mice, that microbes influence the gut's own serotonin system. It says nothing directly about mood, and it can't, because the serotonin it measured was outside the brain.

Microbes that make neurotransmitters themselves

A **microbe-made neurotransmitter** is a chemical produced by bacteria or other microbes that is the same molecule the human body uses as a neurotransmitter, such as GABA, dopamine, or serotonin. A 2018 review by Philip Strandwitz describes gut bacteria that produce or consume dopamine, norepinephrine, serotonin, and GABA.

The best-studied example is GABA. In 2019, Strandwitz and colleagues reported in *Nature Microbiology* that some very common human gut bacteria, especially *Bacteroides* species, made large amounts of GABA in lab cultures, and that GABA-making genes were actively used by bacteria in stool samples from healthy people. For dopamine, a 2022 review by Hamamah and colleagues describes gut microbes taking part in dopamine chemistry, but mostly from lab and animal studies.

Two cautions keep this honest. First, "bacteria can make GABA" is not the same as "bacterial GABA reaches your brain." Most such molecules act locally in the gut or on gut nerves, and the sources in this chapter don't show microbial GABA or dopamine crossing into the human brain. Second, the human mood evidence is correlational. In 2019, Mireia Valles-Colomer, Jeroen Raes, and colleagues studied the gut microbes of 1,054 people in Belgium's Flemish Gut Flora Project and checked the results in other data sets of about 1,000 more people. Certain butyrate-making bacteria were linked to better quality of life, and two groups of bacteria (*Coprococcus* and *Dialister*) were lower in people with depression, even after the researchers accounted for antidepressant use. The authors stressed how much confounding factors matter, and a study like this shows a link, not a cause.

A 2021 review by Kara Margolis, John Cryan, and Emeran Mayer sums up the field: animal studies of the microbiota-gut-brain axis have shown much promise, but they haven't yet been turned into proven diagnoses or treatments for patients.

Hype Meter: "Gut bacteria make neurotransmitters that reach your brain"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype, as stated. The first half is real: it's well shown in lab cultures that common gut bacteria make GABA and other neurotransmitter molecules, and in mice that bacteria raise the gut's own serotonin production. But the "reach your brain" part is not shown in people: most of these molecules act in the gut, and human links between microbes and depression (about 1,000 people in one major study) are correlations. **What would change the grade:** Human studies tracing a microbe-made molecule from the gut into the brain, followed by controlled trials showing that changing those microbes changes brain chemistry and mood.

At the Bedside: Stomach Trouble on a New Medicine

Meet the patient (fictional)

Jordan is 15 and has been seeing a psychiatrist for depression for two months, alongside weekly therapy. Jordan recently started an SSRI. In the first two weeks, Jordan has felt queasy most mornings, had loose stools a few times, and hasn't noticed any change in mood yet. Jordan's mom wonders if the medicine is "messing up Jordan's stomach" and whether to stop it.

What the doctor checks: The psychiatrist asks when the stomach symptoms started compared with the first dose, how bad they are, whether Jordan can eat and drink normally, and whether there is fever, blood in the stool, or severe pain that might point to something else, like an infection. The doctor also checks in carefully about mood, sleep, and any thoughts of self-harm, because the first months of treatment need close watching in teens.

Connecting the signals: The timing fits a known effect. The SSRI blocks the serotonin transporter in the brain, which is the goal, but also on the gut's lining cells. Gut serotonin from enterochromaffin cells lingers longer near nerve endings, which can trigger nausea signals through the vagus nerve and speed up gut movement.

Diagnosis: Common early gastrointestinal side effects of an SSRI.

Why it happens: Gut and brain use the same molecule and the same kind of pump, even though their serotonin supplies are separate (Sections 5.6 and 5.9). A medicine in the bloodstream reaches both.

The mind-body side: Feeling sick to your stomach while also waiting weeks for a mood medicine to work is discouraging, and it can make teens want to quit. The psychiatrist explains that early stomach effects are common and worth reporting, that the full benefit can take several weeks, and that stopping suddenly can cause its own symptoms. Jordan's therapist helps Jordan track symptoms without catastrophizing, and the family agrees on a plan for who to call if mood worsens. The doctor also reminds them that 988 is available any time in a crisis.

Treatment today: Depression in teens is commonly treated with therapy, medicine, or both. Any change to an SSRI, such as timing, dose, or switching medicines, is decided with the prescriber, not at home. The care team may suggest practical steps for nausea and will watch whether side effects fade over the first weeks.

What's new in research: Scientists have developed drugs that block tryptophan hydroxylase to lower serotonin production outside the brain; Mawe and Hoffman's 2013 review describes versions designed not to cross the blood-brain barrier. In February 2017, the FDA approved telotristat ethyl (Xermelo), a tryptophan hydroxylase blocker that lowers serotonin production, for adults with carcinoid syndrome diarrhea, taken together with somatostatin analog therapy when that therapy alone doesn't control it. (Carcinoid syndrome is caused by tumors that release too much serotonin.) A 4-week placebo-controlled trial of a related compound, LX-1031, in 155 people with non-constipating IBS found some symptom relief, but the improvement on its main measure was statistically clear only in the first week (Brown and colleagues, 2011). The drug's maker ran that trial, and LX-1031 has not been approved for any use. **Evidence grade: Preliminary** for IBS (one small, short, company-run trial).

Your turn: reason through a variation

A few weeks later, Jordan's stomach symptoms have faded and mood is starting to improve. Jordan's aunt says, "See, the medicine fixed the serotonin in Jordan's gut, and that's what made Jordan happier." What's wrong with that explanation?

Answer: The stomach side effects came from the SSRI acting on the gut's serotonin system, but mood improvement doesn't come from gut serotonin, which can't cross the blood-brain barrier. The SSRI acts separately in the brain, where neurons make their own serotonin from tryptophan, and its benefits likely build up through changes in brain circuits over weeks. Therapy, time, and support may also have helped. The gut effects and the mood effects happen in two different "towns."

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Serotonin made in the gut travels to the brain and boosts mood.
Reality: Gut serotonin does not cross the blood-brain barrier. The brain makes its own serotonin from tryptophan, which can cross. Gut serotonin mainly works in the gut and is stored in platelets.

Myth: Serotonin is just the "happy chemical."
Reality: Serotonin does many jobs: gut movement, nausea signals, blood clotting, and in the brain, sleep, appetite, pain, and more. Mood is only one of its roles.

Myth: Low serotonin is proven to cause depression.
Reality: A 2022 umbrella review found no consistent evidence for that simple cause. Other scientists argue that serotonin still plays a part in some people, and that debate continues. Depression has many causes, and the debate is separate from whether antidepressants help.

Myth: Gut microbes "make your mood."
Reality: Some gut bacteria make GABA and other neurotransmitter molecules in the lab, and in mice some raise gut serotonin. Whether these chemicals reach the human brain and change mood has not been shown; human links are correlations.

Myth: Eating foods with serotonin, like bananas, raises brain serotonin.
Reality: Serotonin in food can't cross the blood-brain barrier any better than gut serotonin can.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Your gut makes 95% of your serotonin! This probiotic boosts gut serotonin so you'll feel calmer and happier in two weeks."

Grade: Hype. The "95%" figure is within the range scientists report (more than 90%, some estimates about 95%). But gut serotonin can't cross the blood-brain barrier, so raising it wouldn't raise brain serotonin. The best evidence that bacteria boost gut serotonin comes from mice (Yano 2015), and it measured gut and blood serotonin, not mood. A careful version: "Most of your serotonin is made in your gut, where it controls digestion; in mice, some gut bacteria increase that production."

2. Predict: Riya's grandmother hears that tryptophan is the building block of serotonin and wonders if a big turkey dinner will flood Riya's brain with serotonin. Predict what actually happens to the tryptophan, using this chapter.

Most of the tryptophan will be used for building proteins or broken down by the kynurenine pathway; more than 95% of dietary tryptophan goes that way. The part that reaches the blood-brain barrier has to compete with other large neutral amino acids for the same transporter. Only a small amount enters the brain and becomes serotonin, so one meal won't "flood" the brain. The body regulates this closely.

3. Explain: Why can an SSRI cause nausea even though it's prescribed for the brain?

An SSRI blocks the serotonin transporter everywhere the drug reaches, not just in the brain. The gut lining's cells and platelets also use SERT to clear serotonin. With SERT blocked, serotonin released by enterochromaffin cells lingers near sensory nerve endings, which can send nausea signals through the vagus nerve and change gut movement.

4. Apply: A drug company designs a TPH1 blocker that can't cross the blood-brain barrier. Predict its effect on gut serotonin, blood serotonin, and brain serotonin.

Gut serotonin should fall, because EC cells use TPH1. Blood serotonin should fall too, since platelets get their serotonin from the gut. Brain serotonin should stay about the same, because brain neurons use TPH2 and the drug can't get into the brain anyway. That's the idea behind the TPH inhibitors described in Mawe and Hoffman's review, and it's a good test of the two-supplies model.

5. Read the data. The "90%" figure appears in many sources. Here are the estimates from three sources cited in this chapter, along with the kind of paper each one is:

Source	Type	Share of the body's serotonin in or made by the gut
Gershon, 2013	Review	About 95% located in the gut

Source	Type	Share of the body's serotonin in or made by the gut
Yano et al., 2015	Mouse study (cites earlier work)	More than 90% made in the gut
Bellono et al., 2017	Mouse and cell study (cites earlier work)	EC cells make more than 90%

5. What does this data show, and what can't it show?

It shows that independent sources agree the gut makes or holds the large majority of the body's serotonin, somewhere between more than 90% and about 95%, so the "90%" number is solid. It can't show anything about mood, because none of these numbers measures brain serotonin or happiness; they describe where serotonin is made. It also doesn't tell us how much varies between people. A useful follow-up would be a human study measuring gut serotonin production, blood serotonin, and brain serotonin activity in the same people to confirm how separate the two supplies are.

Exercises

Remember

1. Name the enzyme that starts serotonin production, and say which version works in the gut's EC cells and which works in brain neurons.

Answer

Tryptophan hydroxylase (TPH). TPH1 works in enterochromaffin cells; TPH2 works in neurons, including the brain's serotonin neurons.

1. List the three fates of serotonin released by an enterochromaffin cell.

Answer

It acts on nearby nerve endings, it is taken back into lining cells by the serotonin transporter (SERT), or it enters the blood, where platelets store it.

Understand

1. Explain the two-towns comparison in your own words, naming what the valley, hilltop, wall, bread, and flour each stand for.

Answer

The valley is the gut, which makes most of the body's serotonin; the hilltop is the brain, which makes its own. The wall is the blood-brain barrier. The bread is serotonin, which can't get through the wall. The flour is tryptophan, which passes through transporter "gates" so the brain can make its own serotonin.

1. Explain why a signal from gut serotonin can reach the brain even though the serotonin molecule itself cannot.

Answer

Gut serotonin activates vagus and spinal sensory nerve endings in the gut wall. Those nerves carry electrical signals up to the brainstem. The information travels; the molecule stays in the gut.

Apply

1. Use the MicroSim to compare the counter values after five presses of "Release gut serotonin" with and without the SSRI box checked. Describe what changed and connect it to a real SSRI side effect.
2. A supplement label says "Contains 5-HTP and tryptophan to boost serotonin naturally!" Using this chapter, identify which parts of the claim are plausible chemistry and which parts are unsupported, and give it a Hype Meter grade. (Don't evaluate whether anyone should take it; that's a question for a doctor.)

Analyze

1. Compare the evidence in the Yano 2015 mouse study and the Valles-Colomer 2019 human study. For each, answer at least three of the six questions. Which is better at showing cause, and which tells you more about people?
2. Sam's cousin's post has three links (Section 5.8). Analyze a different gut-brain claim you've seen online (or make a realistic one up) by breaking it into links and grading each link separately.

Evaluate

1. Some people argue the Moncrieff 2022 review shows antidepressants don't work. Evaluate this argument using what the review did and didn't test.
2. Should the phrase "your gut makes 90% of your serotonin" be used in health class at all? Write a paragraph weighing the value of the fact against how often it's misused, and propose the exact sentence you would

teach.

Create

1. Design a study in humans that could test whether a probiotic changes brain serotonin, not just gut serotonin. Describe the groups, how you would measure brain serotonin activity (in general terms), how long it would last, and what result would support the claim.
2. Create a 30-second video script that corrects the gut serotonin mood myth for a teen audience without making people feel foolish for having believed it.

Key Takeaways

- Neurons pass messages at synapses using neurotransmitters such as serotonin, dopamine, GABA, and acetylcholine; the same chemical can act as a neurotransmitter or a hormone.
- More than 90% of the body's serotonin is made in the gut, mostly by enterochromaffin cells using TPH1. Gut serotonin runs gut movement, secretion, and nausea signals, is cleared by the serotonin transporter, and is stored in platelets.
- Serotonin made in the gut does not cross the blood-brain barrier. The brain makes its own serotonin from tryptophan, an amino acid that can cross, using TPH2. Most dietary tryptophan goes down the kynurenine pathway instead.
- "90% of your serotonin is in your gut, so your gut controls your happiness" is Hype: the number is Strong, the conclusion is not.
- SSRIs block the serotonin transporter in both brain and gut, which is why early nausea or loose stools are common. Changes to any medicine are decided with the prescriber.
- "Depression is caused by low serotonin" is too simple for the evidence; that debate is separate from whether antidepressants help.
- Gut bacteria can make neurotransmitter molecules and, in mice, boost gut serotonin, but evidence that microbe-made chemicals reach the human brain and change mood is Preliminary.

You followed serotonin all the way!



You can now trace serotonin from tryptophan to the gut, the blood, and the wall it can't cross, and you can grade the internet's favorite gut-brain fact link by link. Next, in Chapter 6, we'll follow what your microbes make from fiber, and look closely at the blood-brain barrier and the "leaky gut" claim.

Quiz: Chemical Messengers and the Serotonin Myth

Test your understanding of Chapter 5. Choose the best answer, then click **Show Answer** to check.

Question 1

Which cells make most of the body's serotonin?

A. Serotonin neurons in the brainstem

B. Platelets in the blood

C. Enterochromaffin cells in the gut lining

D. Gut bacteria in the colon

Show Answer

The correct answer is **C**. More than 90% of the body's serotonin is made in the gut, mostly by enterochromaffin (EC) cells, even though they are less than 1% of the gut's lining cells. Platelets (option B) store serotonin from the gut but don't make it.

Concept Tested: Enterochromaffin Cell **Bloom's Level:** Remember

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Question 2

What is tryptophan?

A. An essential amino acid from food that the body uses to make serotonin

B. An enzyme that breaks serotonin down in the brain

C. A type of gut bacterium that produces serotonin

D. A medicine that blocks the serotonin transporter

Show Answer

The correct answer is **A**. Tryptophan is an essential amino acid, so it must come from protein in food, and it is the raw material for serotonin. Option B mixes it up with enzymes; the enzyme that turns tryptophan into serotonin is tryptophan hydroxylase.

Concept Tested: Tryptophan **Bloom's Level:** Remember

Question 3

Which neurotransmitter is the brain's main inhibitory ("brake") signal?

A. Acetylcholine

B. Dopamine

C. Serotonin

D. GABA

Show Answer

The correct answer is **D**. GABA mostly makes receiving neurons less likely to fire. Acetylcholine (option A) is a main "go" signal for gut muscle and is released by enteric motor neurons and the vagus nerve's motor fibers.

Concept Tested: GABA **Bloom's Level:** Remember

Question 4

Why can't serotonin made in the gut raise serotonin levels in the brain?

A. The liver turns all gut serotonin into tryptophan.

B. Serotonin cannot cross the blood-brain barrier, so the brain makes its own from tryptophan.

C. Gut serotonin is a different molecule from brain serotonin.

D. The vagus nerve blocks serotonin from traveling upward.

Show Answer

The correct answer is **B**. The blood-brain barrier keeps gut serotonin out, and brain neurons make their own serotonin from tryptophan, which can cross. Option C is a common mix-up: it's the same molecule (5-HT) in both places; what differs is where it's made and where it can travel.

Concept Tested: Blood-Brain Barrier **Bloom's Level:** Understand

Question 5

Why do scientists say the body has two separate serotonin supplies?

A. Gut EC cells use TPH1, brain neurons use TPH2, and the blood-brain barrier keeps the two pools apart.

B. Men and women make different kinds of serotonin.

C. Serotonin made in the morning and at night comes from different organs.

D. Platelets make one supply and gut bacteria make the other.

Show Answer

The correct answer is **A**. Two versions of tryptophan hydroxylase work in two places, TPH1 in EC cells and TPH2 in neurons, and the blood-brain barrier separates the gut and blood pool from the brain pool. Option D is wrong because platelets store gut serotonin rather than make it.

Concept Tested: Tryptophan Hydroxylase **Bloom's Level:** Understand

Question 6

What does the serotonin transporter (SERT) do in the gut lining?

A. It carries serotonin across the blood-brain barrier into the brain.

B. It makes serotonin from tryptophan inside EC cells.

C. It pumps serotonin back into cells, ending its signal.

D. It releases serotonin into the gut to trigger peristalsis.

Show Answer

The correct answer is **C**. SERT is a pump that clears serotonin by moving it back into cells; in the gut it is found on essentially all lining cells, and platelets use it too. Option B describes the job of tryptophan hydroxylase, not SERT.

Concept Tested: Serotonin Transporter **Bloom's Level:** Understand

Question 7

A 16-year-old starts an SSRI for anxiety and has nausea and loose stools in the first two weeks. Which explanation best fits this chapter?

A. The medicine sends brain serotonin down into the gut.

B. The medicine kills helpful gut bacteria that make serotonin.

C. Nausea means the medicine isn't reaching the brain at all.

D. The medicine also blocks SERT in the gut, so gut serotonin lingers near nerves that control movement and nausea.

Show Answer

The correct answer is **D**. SSRIs reach the whole body, and the gut lining and platelets use SERT too. Blocking it leaves gut serotonin active longer near sensory nerves. Option A is backwards: brain serotonin doesn't travel to the gut, just as gut serotonin doesn't travel to the brain. Any change to the medicine should be decided with the prescriber.

Concept Tested: SSRI **Bloom's Level:** Apply

Question 8

A friend says, "I'm going to eat a lot of turkey so all that tryptophan turns into serotonin in my brain." Using this chapter, what is the best response?

A. Right, nearly all tryptophan becomes brain serotonin within an hour.

B. Most tryptophan goes to the kynurenine pathway and protein building, and what reaches the brain competes with other amino acids to cross.

C. Tryptophan can't cross the blood-brain barrier, so none of it reaches the brain.

D. Tryptophan only becomes serotonin in the gut, never in the brain.

Show Answer

The correct answer is **B**. More than 95% of dietary tryptophan is broken down through the kynurenine pathway, and tryptophan competes with other large neutral amino acids for the transporter into the brain. Option C goes too far the other way: tryptophan can cross, which is how the brain makes its own serotonin.

Concept Tested: Kynurenine Pathway **Bloom's Level:** Apply

Question 9

In the Yano et al. (2015) study, spore-forming bacteria given to germ-free mice raised serotonin in the colon and blood. Which conclusion does this study best support?

A. Spore-forming bacteria cure depression in people.

B. Gut bacteria control the amount of serotonin in the human brain.

C. In mice, certain gut bacteria increase the gut's own serotonin production.

D. The gut serotonin mood myth has been proven true.

Show Answer

The correct answer is **C**. The study was done in mice and measured gut and blood serotonin, which can't enter the brain, so it says nothing directly about brain serotonin or mood. Option B is the overstatement often made in ads: it jumps from mice to people and from gut serotonin to brain serotonin.

Concept Tested: Spore-Forming Bacteria **Bloom's Level:** Analyze

---

Question 10

A post says: "Gut bacteria make GABA, the brain's calming chemical, so the right bacteria will calm your anxiety." Which analysis is most accurate?

A. Some gut bacteria make GABA in lab cultures, but it hasn't been shown that microbial GABA reaches the human brain or calms anxiety.

B. The post is fully proven, because GABA from any source enters the brain easily.

C. The post is impossible, because no bacteria can make GABA.

D. The post is proven by the human study that found Coprococcus lower in depression.

Show Answer

The correct answer is **A**. Strandwitz and colleagues showed that common gut bacteria such as *Bacteroides* make large amounts of GABA in culture, but most such molecules act locally in the gut, and the human evidence linking microbes to mood is correlational. Option D treats a correlation in a human study as proof of cause, which it isn't.

Concept Tested: Microbe-Made Neurotransmitter **Bloom's Level:** Analyze

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Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier

Summary

The fiber in beans, grains, fruits, and vegetables passes through your small intestine without being digested. In the colon, gut bacteria ferment it and make short-chain fatty acids, mainly acetate, propionate, and butyrate. This chapter follows those molecules: butyrate fuels the cells that line your colon, all three act on receptors and even on how genes are switched on, and some travel in the blood. It then looks at the gut barrier, the real science of intestinal permeability, and why "leaky gut syndrome" is not a recognized diagnosis. Finally, it asks whether these microbial molecules reach the brain, where the best evidence (on microglia and the blood-brain barrier) still comes from mice.

Concepts Covered

1. Dietary Fiber
2. Fermentation
3. Short-Chain Fatty Acid
4. Butyrate
5. Propionate
6. Acetate
7. Colonocyte
8. Free Fatty Acid Receptor
9. Gene Regulation by Butyrate
10. Intestinal Permeability
11. Leaky Gut Claim
12. Zonulin
13. Lipopolysaccharide
14. Metabolic Endotoxemia
15. Microglia Maturation
16. BBB Permeability

Prerequisites

- Chapter 3: Meet the Microbiome (gut microbiota, microbial diversity, germ-free mice, correlation vs causation)
- Chapter 4: The Immune System as a Sense Organ (intestinal epithelium, tight junctions, regulatory T cells, microglia)
- Chapter 5: Chemical Messengers and the Serotonin Myth (the blood-brain barrier)

Following the leftovers



Some of the most interesting gut-brain science starts with the part of your food that you can't digest. In this chapter we'll follow fiber all the way from a pot of lentils to the cells of your colon, and then ask a harder question: does anything made from it reach the brain? Along the way you'll meet "leaky gut," one of the most popular claims online, and find out which parts of it are real.

6.1 What Happens to the Beans You Can't Digest?

On Sunday afternoons, Riya cooks with her grandmother. Today it's dal: yellow lentils simmered until soft, then finished with a sizzling spoonful of cumin, garlic, and chili in hot ghee. Her grandmother never measures anything. Riya, who has Crohn's disease and has spent two years learning more about her gut than she ever wanted to, stirs the pot and asks a question her grandmother can't answer: "Most of this gets digested, right? But what happens to the part that doesn't?" (Riya is a fictional student who appears throughout this book.)

It's a better question than it sounds. Your small intestine absorbs most of the starch, protein, and fat in that bowl of dal. But lentils also contain fiber, which your own body has no enzymes to break down. That fiber rides on into the colon, where trillions of microbes are waiting. They eat it, and in the process they make small molecules that soak into your colon wall, enter your blood, and, in mice at least, influence cells inside the brain. This chapter follows that journey step by step, and at each step it asks the Hype Meter question: is this shown in people, or only in mice?

6.2 Dietary Fiber: Food for Your Microbes

Imagine you and a roommate share a kitchen. You cook dinner, eat what you like, and leave the rest on the counter. Your roommate, who has tools you don't have, turns your leftovers into something new, and some of it comes back to you as a gift. Fiber works a bit like those leftovers. You can't use it yourself, but the microbes in your colon can, and they hand back some useful products.

Dietary fiber is the part of plant foods that human digestive enzymes can't break down, so it reaches the large intestine mostly intact. MedlinePlus, the US National Library of Medicine's health site, describes fiber as a type of carbohydrate found in fruits, vegetables, grains, and legumes (beans, lentils, and peas). Because it isn't fully digested, fiber provides only about half the calories per gram of other carbohydrates.

Not all fiber is the same. MedlinePlus sorts it into two broad forms:

Type	What it does in water	Where you find it	What it does in the gut
Soluble fiber	Attracts water and forms a gel	Oat bran, barley, nuts, seeds, beans, lentils, peas, some fruits and vegetables	Slows digestion
Insoluble fiber	Doesn't dissolve	Wheat bran, vegetables, whole grains	Adds bulk to stool and helps move contents along

Most high-fiber foods contain both kinds. Riya's lentils are rich in soluble fiber, while the whole-wheat roti her grandmother serves alongside adds insoluble fiber. Scientists also describe fibers by how *fermentable* they are, meaning how easily microbes can break them down, and fibers differ a lot in this. Starch that escapes digestion in the small intestine (called resistant starch) is also fermented in the colon. The two-column table is a useful start, but "fiber" is really a family of very different molecules.

How much fiber do people eat? According to MedlinePlus, Americans average about 16 grams a day. The 2020 to 2025 Dietary Guidelines for Americans suggested about 25 grams a day for girls aged 14 to 18 and about 31 grams for boys of the same age. The newer *Dietary Guidelines for Americans, 2025 to 2030* (released in January 2026) don't give a gram target; they encourage high-fiber and minimally processed foods instead.

Those are population guidelines, not personal prescriptions. People with some gut conditions get different advice from their care teams, and that's a conversation to have with a doctor or dietitian, not something to change on your own.

For families

Food carries love, culture, and memory, like Riya's Sunday dal. This chapter is about what microbes do with fiber, not about "good" or "bad" foods. If your teen has a gut condition, their care team may give them food advice that's different from general guidelines, and it helps to follow that plan without commenting on their plate. A useful question at dinner is "What would make eating easier for you right now?" rather than "Should you be eating that?"

6.3 Fermentation: Your Colon's Microbial Kitchen

When you hear "fermentation," you might picture yogurt, kimchi, or bread dough rising. Those all involve microbes breaking down sugars without much oxygen and making new products, like acids or gas. Your colon does the same thing every day, on a much larger scale.

Fermentation is the process in which microbes break down carbohydrates without oxygen, releasing energy for themselves and leaving behind products such as gases and short-chain fatty acids. The colon is a good place for it. It has very little oxygen, food moves slowly, and it is home to most of your gut microbes (you met them in Chapter 3).

Where exactly does it happen? A classic 1987 study by Cummings and colleagues answered this in an unusual way. The team measured short-chain fatty acids in the intestines and blood of people who had died suddenly, sampled within four hours of death. The concentration was low at the end of the small intestine (about 13 mmol per kilogram of contents) but high throughout the colon, highest in the first part, the cecum (about 131), and lower farther along in the descending colon (about 80). The colon contents were also most acidic in the cecum (pH about 5.6) and less acidic farther down (about 6.6), because those acids pile up where fermentation is busiest. The authors concluded that most fermentation in people happens in the cecum and ascending colon, the first stretch of the large intestine.

Fermentation also makes gas, which is why a big, sudden jump in fiber can cause gas, bloating, and cramps. MedlinePlus notes that these problems often settle as the gut's bacteria adjust, which is one reason dietitians suggest adding fiber gradually. Gas from fermentation is a normal sign that your microbes are working, not a sign of damage.

Same fiber, different kitchens



I find it amazing that two people can eat the same bowl of dal and make different amounts of each fermentation product. What gets made depends on which microbes are in your kitchen, and that's one reason diet studies in people give such mixed results.

6.4 Three Short-Chain Fatty Acids

Fermentation produces many things, but three molecules get the most attention. A **short-chain fatty acid** (SCFA) is a small fatty acid, with a chain of no more than six carbon atoms, made mainly when gut microbes ferment fiber and resistant starch. A 2016 review in the journal *Cell* by Koh and colleagues calls SCFAs a major class of bacterial products that can act on receptors, change how genes are switched on, and serve as fuel. The big three are:

- **Acetate** is the two-carbon SCFA and usually the most abundant. It travels the farthest, passing through the liver and reaching the rest of the body in the blood.
- **Propionate** is the three-carbon SCFA. Much of it is taken up by the liver before it can reach the rest of the body.
- **Butyrate** is the four-carbon SCFA. Most of it never leaves the gut wall, because the cells lining the colon use it as fuel.

You may see a fixed ratio of these three quoted online. The amounts actually vary from person to person and from one part of the colon to another, so this book just says that acetate is usually the most plentiful.

The Cummings study showed where each one goes in the human body. The researchers measured SCFAs in three kinds of blood: the portal vein (which carries blood from the gut straight to the liver), the hepatic vein (blood leaving the liver), and ordinary blood in the arm (peripheral blood).

Where the sample came from	Total SCFAs (micromoles per liter)
Portal vein (gut to liver)	about 375
Hepatic vein (leaving the liver)	about 148
Peripheral blood (rest of body)	about 79

Total SCFAs drop at each step, because cells keep using them. The mix also shifted along the way: the colon lining took up more butyrate, the liver took up more propionate, and acetate was the main SCFA in every sample. So the gut wall gets most of the butyrate, the liver gets much of the propionate, and the rest of the body, including the brain's blood supply, sees mostly acetate.

SCFA	Carbon atoms	Main destination	Example roles in research
Acetate	2	Rest of the body via blood	Most abundant in blood; used as fuel by many tissues
Propionate	3	Liver	Mostly removed by the liver; also signals through receptors
Butyrate	4	Colon-lining cells	Main fuel for colonocytes; affects gene activity and immune cells

6.5 Butyrate and the Colonocyte

Most cells in your body get their energy from fuels delivered by the blood, such as glucose and fats. The cells lining your colon are unusual: they get much of their energy from the colon's contents, delivered by microbes.

A **colonocyte** is one of the epithelial cells that line the inside of the colon. Colonocytes absorb water and salts and help form the barrier between the gut contents and the body. (The barrier itself, with its mucus and tight junctions, was introduced in Chapter 4.)

The clearest experiment on colonocyte fuel comes from mice. In 2011, Donohoe and colleagues compared colonocytes from germ-free mice (raised with no microbes at all) with those from normal mice. The germ-free colonocytes were in an energy-starved state: their power plants (mitochondria) were making less energy, and the cells had started breaking down their own parts to survive, a process called autophagy. When the researchers added butyrate, the starved cells recovered. The team concluded that in mice, colonocytes use bacterial butyrate as their primary energy source. The human autopsy data fit this picture, since the human colon lining took up butyrate more than the other SCFAs. So do lab studies of human cells.

In 1980, Roediger tested colonocytes taken from 14 surgery specimens of human colon: when butyrate was the only fuel offered, about three-quarters of the cells' oxygen use went to burning it, and butyrate stayed a major fuel even when glucose was also available (Roediger 1980).

Germ-free mice are an extreme case, though. They show what happens when microbes are completely missing, not what happens when a person eats a little less fiber one week.

Butyrate also appears to do more than feed cells. In mice, SCFAs, and butyrate in particular, help the colon build up regulatory T cells, the immune cells that calm inflammation. Two 2013 papers showed this: Smith and colleagues in *Science* found that SCFAs regulated the size and function of the colon's regulatory T cell population and protected mice against colitis (colon inflammation), and Furusawa and colleagues in *Nature* found that butyrate drove immature T cells to become regulatory T cells and reduced colitis in a mouse model. These are mouse findings. They help explain why scientists are interested in butyrate for inflammatory bowel disease, but they don't show that eating more fiber treats Crohn's disease or ulcerative colitis in people.

Hype Meter: "Butyrate helps protect the gut lining"

Strong	**Moderate**	Preliminary	Hype

Verdict: Moderate. In mice, butyrate is the main fuel for colonocytes (Donohoe 2011) and helps build calming regulatory T cells that protect against colitis (Smith 2013; Furusawa 2013). In people, the evidence is real but small: the colon lining takes up butyrate preferentially (Cummings 1987, autopsy data), colon cells from surgery specimens burn it as a main fuel (Roediger 1980, lab study), and in 4 patients with diversion colitis (inflammation in a stretch of colon cut off from the stool stream after surgery) rinsing that stretch with SCFAs cleared the inflammation over four to six weeks (Harig 1989). But a later double-blind trial in 13 patients found that two weeks of SCFA rinses worked no better than salt water (Guillemot 1991). What's missing is strong evidence from larger human trials that raising butyrate improves the gut lining or prevents disease. **What would change the grade:** Randomized trials in people showing that raising colon butyrate (through diet or another route) improves measured barrier function or disease outcomes would move this up. Trials showing no effect would move it down.

6.6 How SCFAs Send Messages: Receptors and Genes

Fuel is only part of the story. SCFAs also work as signals, and they do it in two different ways. Think of a building with a doorbell and a dimmer switch. A visitor can ring the doorbell from outside, or someone inside can turn the lights up or down. SCFAs can do both.

The doorbell: receptors. A **free fatty acid receptor** is a protein on the surface of a cell that detects fatty acids outside the cell and passes a signal inside. Two of them respond to SCFAs. They were first called GPR43 and GPR41, and were later renamed free fatty acid receptor 2 (FFAR2) and free fatty acid receptor 3 (FFAR3), according to a 2020 review by Silva, Bernardi, and Frozza in *Frontiers in Endocrinology*. These receptors sit on many cell types, from the gut lining to immune cells and nerve cells. When SCFAs bind them on enteroendocrine cells (the hormone-making cells of the gut lining you met in Chapter 2), the cells release gut hormones such as GLP-1 and peptide YY. Those hormones can then signal through the blood or the vagus nerve. FFAR2 shows up again and again in this chapter: the mouse studies on regulatory T cells and on brain immune cells both found that the receptor was needed for the effects.

The dimmer switch: genes. Inside every cell nucleus, DNA is wrapped around spool-like proteins called histones. When DNA is wound tightly, genes in that stretch are harder to read; when it's loosened, they're easier to switch on. Cells use small chemical tags called acetyl groups to loosen the wrapping, and they use enzymes called histone deacetylases (HDACs) to remove those tags again. **Gene regulation by butyrate** is butyrate's ability to block histone deacetylases, which leaves more acetyl tags on histones and changes which genes a cell turns on. Koh and colleagues list HDAC inhibition as one of the three main ways SCFAs act.

Here's a concrete example from mice. In the Furusawa study, butyrate increased acetyl tags on histones at the *Foxp3* gene, the master switch that makes a T cell become a regulatory T cell. That suggests a chain: microbes ferment fiber, butyrate is made, butyrate loosens the DNA at *Foxp3*, and more calming immune cells develop. In colonocytes, though, the Donohoe team found that butyrate's rescue effect worked mainly through fuel, not through HDAC blocking. The same molecule can act differently in different cells.

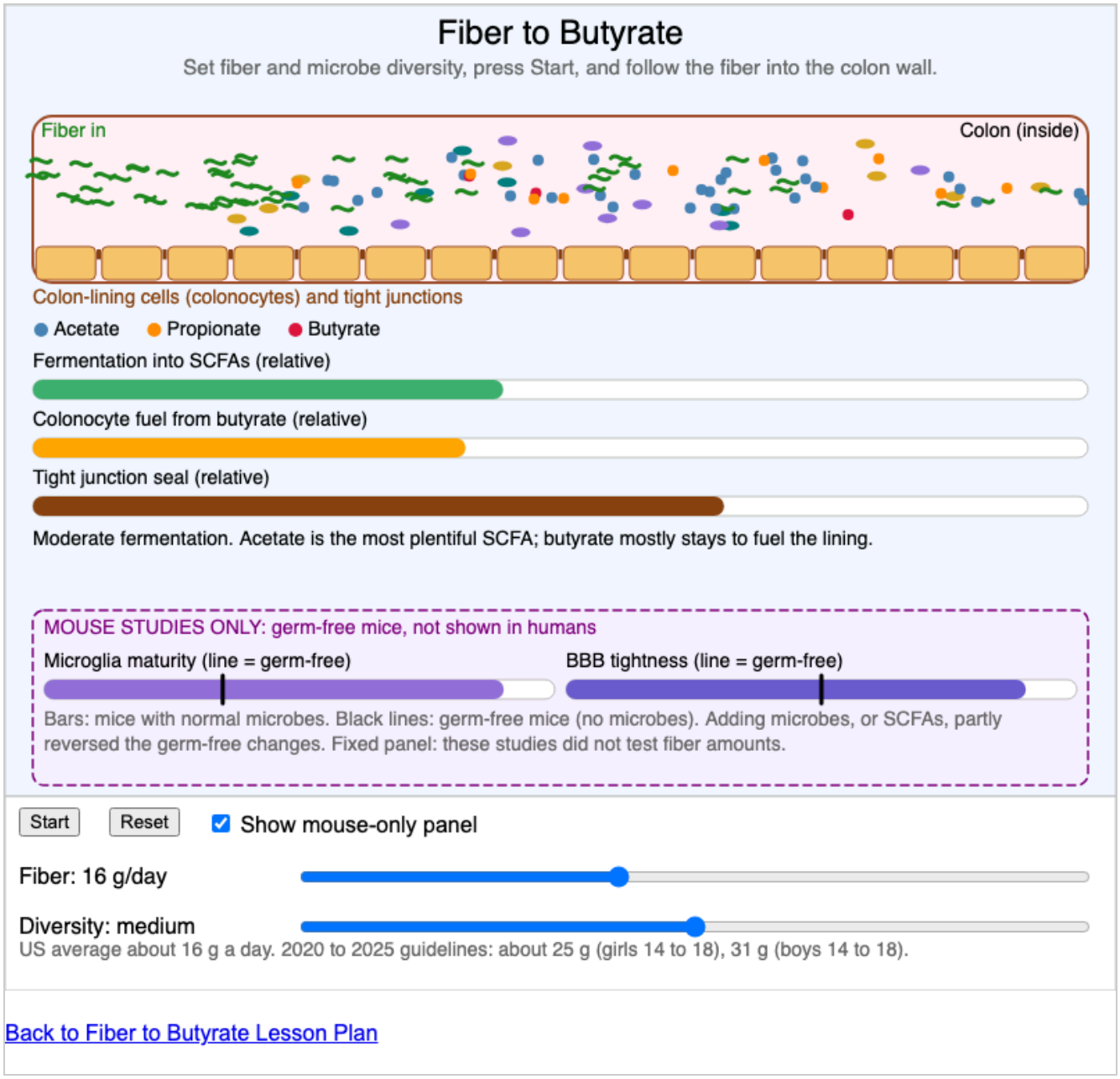
Two jobs, one molecule



If histones and HDACs feel like a lot, hang in there: you only need the big idea. Butyrate can ring a doorbell on the outside of a cell (a receptor) or reach inside and turn a dimmer switch on genes (HDAC blocking), and different cells listen in different ways.

Now you can follow the whole path in a model. Use the MicroSim below to trace fiber from the moment it enters the colon to the cells of the colon wall.

Diagram: Fiber to Butyrate



Back to Fiber to Butyrate Lesson Plan

Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch06-fiber-to-butyrate/main.html

Open the Fiber to Butyrate fullscreen

MicroSim specification: Fiber to Butyrate

Type: microsim **sim-id:** ch06-fiber-to-butyrate
Library: p5.js
Status: Implemented
Bloom Level: Understand
Bloom Verb: trace
Learning Objective: The learner will trace dietary fiber through bacterial fermentation to acetate, propionate, and butyrate and their effects on colonocytes and tight junctions, and distinguish these from brain effects shown only in mice.

Canvas: 570 px drawing area plus 140 px controls (iframe 712 px); responsive to about 380 px wide.

Controls: Start/Pause, Reset, Show mouse-only panel (checkbox, default on); Fiber slider (0 to 40 g/day, step 1, default 16); Microbe diversity slider (5 steps from very low to very high, default medium).

Rules: Fermentation rises with fiber and levels off at high intakes; more microbe diversity raises fermentation capacity and the share of butyrate. Acetate is always the most plentiful SCFA drawn; butyrate particles move into the colon wall. Colonocyte fuel follows butyrate; tight junction seal rises with fuel but never drops to zero, because other factors also maintain it. The mouse-only panel is fixed: bars show microglia maturity and blood-brain barrier tightness in mice with normal microbes, and black lines show germ-free mice; it does not respond to the sliders, because those studies compared microbes with no microbes rather than testing fiber amounts. All values are relative and illustrative.

Feedback: A status line describes the fermentation level and where each SCFA goes. Reference marks under the fiber slider show the US average (about 16 g a day) and the 2020 to 2025 guideline values for ages 14 to 18.

Provenance: Sections 6.2 to 6.6 and 6.10 (MedlinePlus fiber page; Cummings 1987; Donohoe 2011; Erny 2015; Braniste 2014). All model numbers are illustrative.

Start at the default of 16 grams a day, about the US average, and press Start. Watch green fiber strands enter on the left and turn into blue acetate, orange propionate, and red butyrate as the bacteria work on them. Notice that only the red butyrate dots drift down into the colon wall, and that the colonocytes glow brighter and the gaps between them narrow as butyrate fuel rises. Now drag the fiber slider to 0, then to 30. Then try the diversity slider: with very low diversity, the same fiber makes less of everything, and especially less butyrate.

Finally, look at the purple dashed panel. It shows two brain effects that have been found **only in germ-free mouse studies**: more mature microglia and a tighter blood-brain barrier when microbes are present (the bars) than when they are absent (the black lines). Move the fiber slider and notice that this panel doesn't change, because those studies compared mice with and without microbes, not different amounts of fiber. Turn the panel off and on, and notice that nothing in the human part of the model depends on it. That separation is the point. Sections 6.7 to 6.10 explain why the boundary matters.

What this model leaves out

- Real fiber is many different molecules, fermented at different speeds by different microbes; the sim treats all fiber as one thing.
- It shows no gas, no protein fermentation, and no other microbial products, and it skips the liver and blood steps that sort acetate and propionate.
- The tight junction seal depends on many things besides butyrate, including the mucus layer, immune cells, inflammation, and medicines; the sim links it only to butyrate, and that link comes mostly from cell and mouse studies.
- The levels are relative teaching numbers, not measurements. Real SCFA amounts vary widely between people and from day to day.
- The mouse panel compares mice with and without microbes. It does not mean that eating more fiber changes a person's microglia or blood-brain barrier.

6.7 The Gut Barrier and Intestinal Permeability

Picture a city with a wall around it. The wall has gates that let in food and trade, and guards who keep out invaders. A wall with no gates would starve the city. A wall with too many holes would let in danger. The gut lining is like that wall. It must let nutrients and water through while keeping microbes and their products out.

A 2017 review by Odenwald and Turner explains that the barrier needs two things: an unbroken layer of epithelial cells, and junctions that seal the narrow spaces between those cells. A 2019 review in *Gut* by Camilleri adds that the full barrier also includes the surface mucus and immune defenses beneath the lining. You met each of those parts in Chapter 4.

Intestinal permeability is how easily substances pass across the gut lining from the inside of the intestine into the body, either through the cells or through the gaps between them. Some permeability is normal and necessary. The question doctors and scientists ask is whether permeability is higher than usual, and whether that matters.

How do you measure something so small? The most common method in people is a sugar test. A person drinks a solution containing two sugars that the body doesn't use, often lactulose (a large sugar that slips through mainly by the gaps) and mannitol (a smaller one that passes more easily). Over the next few hours, both come out in the urine. If the ratio of lactulose to mannitol in the urine rises, more is getting through the gaps, which means permeability is higher. Researchers can also study small tissue samples (biopsies) taken during a scope test.

Camilleri lists several things that increase permeability in people for a while: endurance exercise, common pain relievers called NSAIDs (such as ibuprofen), pregnancy, and some food additives called emulsifiers. Inflammatory diseases that damage the lining, such as Crohn's disease, also increase it. The exercise finding surprises some readers. Sam, Riya's best friend, runs cross-country, and long hard runs can temporarily make

his gut more permeable. That doesn't make running harmful. It shows that permeability goes up and down with normal life, and that a single high measurement isn't a disease. (Sam is a fictional student who appears throughout this book.)

The important limits come from the same reviews. Odenwald and Turner write that most clinical data on barrier loss are correlative, which makes it hard to tell whether a leaky barrier causes a disease or is caused by it. Camilleri adds that inflammatory and ulcerating diseases make the gut leaky, but no such disease can be cured just by normalizing the barrier, and it is still unproven that restoring barrier function improves symptoms. Hold on to that idea. It's the key to the next section.

6.8 "Leaky Gut": Real Measurement, Overblown Claim

Search "leaky gut" online and you'll find thousands of posts. They often go something like this: your gut lining has holes, toxins pour into your blood, and that causes fatigue, brain fog, anxiety, autism, acne, and autoimmune disease. Luckily, the post continues, this powder or test kit can fix it.

The **leaky gut claim** is the popular idea that a condition called "leaky gut syndrome" is a common hidden cause of many symptoms and diseases throughout the body, and that it can be diagnosed with consumer tests and cured with diets or supplements. It mixes a real, measurable thing (intestinal permeability) with a chain of claims that the evidence doesn't support. "Leaky gut syndrome" is not a recognized medical diagnosis.

Let's separate the pieces:

Piece of the claim	What the evidence says	Grade
The gut barrier exists and can become more permeable	True and measurable in people (sugar tests, biopsies)	Strong
Permeability is higher in some diseases, like Crohn's	Yes, but mostly correlation; the disease can cause the leakiness	Strong (link); unclear (cause)
Leaky gut causes autism, depression, and most chronic illness	Not supported by human evidence	Hype
A supplement or diet can "heal" a leaky gut and cure symptoms	No disease has been cured by fixing permeability; diet claims need confirmation	Hype
A blood test for zonulin tells you if your gut is leaky	Common kits don't measure zonulin (see below)	Hype

One molecule appears in many leaky gut ads. **Zonulin** is a protein that some researchers, including the group of Fasano and colleagues, propose loosens tight junctions in the small intestine; it has been reported to be the same molecule as a blood protein called pre-haptoglobin 2. In a 2020 review, Fasano and coauthors present a "structured hypothesis" that a zonulin-driven leaky barrier contributes to autoimmune diseases like celiac disease and type 1 diabetes in genetically at-risk people. A hypothesis is a reasonable idea to test, not a settled fact. (That review discloses that Fasano holds stock in a company and consults for a diagnostics company, which a careful reader notes.)

The bigger problem is the test. In 2018, Scheffler and colleagues measured "zonulin" with a widely used commercial test kit in 376 people. The results didn't match the people's haptoglobin genes, which they should have if the kit measured pre-haptoglobin 2. When the team checked what the kit actually grabbed, it wasn't pre-haptoglobin 2 at all; it detected related proteins instead, most likely one called properdin. In 2019, a separate team in Australia, Ajamian and colleagues, tested two other commercial kits and found they mostly detected haptoglobin and complement C3, other blood proteins. They advised caution about using serum zonulin as a marker of gut barrier health until the tests improve. So a teen who gets a "high zonulin" result from a consumer test may not have learned anything about their gut.

Hype Meter: "Leaky gut causes autism, depression, and everything else"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. Intestinal permeability is real and can be measured, and it rises in some diseases and stressful states. But reviews describe the human data as mostly correlative, no disease has been cured by fixing permeability, and "leaky gut syndrome" is not a recognized diagnosis. Popular zonulin blood tests don't reliably measure zonulin. **What would change the grade:** Large human studies showing that increased permeability comes before a specific condition, plus randomized trials showing that repairing the barrier prevents or improves that condition, could move a narrow version of the claim (one condition, not "everything") toward Preliminary.

6.9 Lipopolysaccharide and Metabolic Endotoxemia

If something does cross a more permeable barrier, what is it? One candidate has been studied closely. Many gut bacteria, the kind called gram-negative bacteria, have an outer coat built partly from a molecule that the immune system recognizes instantly as "bacteria are here."

Lipopolysaccharide (LPS) is a large molecule made of fat and sugar parts that forms much of the outer membrane of gram-negative bacteria; immune cells detect it through pattern recognition receptors (from Chapter 4) and respond with inflammation. Scientists also call LPS endotoxin. In a serious infection, large amounts of LPS in the blood can trigger a dangerous body-wide reaction. But tiny amounts can also show up in the blood normally; in mice, the level rises a bit after meals and falls during fasting.

In 2007, Cani and colleagues studied those tiny amounts in mice. They found that a high-fat diet for four weeks raised the level of LPS in the blood by about two to three times. They named this low but chronic rise **metabolic endotoxemia**: a small, long-lasting increase in blood LPS, linked to diet and gut microbes, that may promote low-grade inflammation and metabolic problems such as insulin resistance. When the researchers infused LPS under the skin of mice for four weeks to copy that rise, the mice developed higher blood sugar and insulin and signs of inflammation in fat tissue, much like the high-fat-fed mice. Mice lacking an LPS-sensing protein called CD14 were protected from most of these changes.

This is strong mouse evidence that small amounts of LPS can drive inflammation and metabolic changes. In people, the picture is less clear. Human studies of blood LPS, diet, and metabolic health are mostly observational, and links like these don't show which came first. For this book's purposes, metabolic endotoxemia is a promising idea with a strong mouse base and still-developing human evidence. It is one reason scientists care about the barrier, not a reason to fear food.

If you're going through this

If you have Crohn's disease, ulcerative colitis, or IBS, you may see posts claiming your illness is "just leaky gut" that a powder can fix. Your condition is real, it's more complicated than that, and your care team treats it with approaches tested in people. Advice about fiber and food can also be different for you than for the general public, so check with your doctor or dietitian before changing what you eat or adding a supplement, even one that sounds harmless.

6.10 From Gut to Brain? Microglia and the Blood-Brain Barrier

Now for the question that put "brain" in this chapter's title. Do SCFAs, or other microbial molecules, change the brain? To answer it, recall two things from earlier chapters. **Microglia** are the brain's resident immune cells (Chapter 4). The **blood-brain barrier** (BBB) is the tightly sealed lining of the brain's blood vessels that controls what passes from the blood into the brain (Chapter 5). For a refresher on glia, see From Neuron to Bedside, Chapter 1.

The BBB works a lot like the gut barrier you just studied, with cells sealed together by tight junction proteins. A 2020 review by Silva and colleagues notes that SCFAs can cross the BBB using transporter proteins, based mostly on animal studies, so they are at least able to reach the brain in small amounts. Two well-known mouse studies looked at what happens when microbes are missing entirely.

Microglia. Microglia maturation is the process by which young microglia develop into fully functional immune cells that can watch over brain tissue and respond to infection or injury. In 2015, Erny, Prinz, and colleagues reported in *Nature Neuroscience* that germ-free mice had widespread microglia defects: their microglia looked and behaved immature, and their innate immune responses were impaired. Giving the mice a complex mix of microbes partly restored the microglia. The team found that SCFAs helped regulate microglia, and mice lacking the SCFA receptor FFAR2 had microglia that looked like those of germ-free mice. According to the

Silva review, giving germ-free mice a mixture of acetate, propionate, and butyrate was enough to drive microglia toward maturity. All of this is in mice.

The blood-brain barrier. BBB permeability is how easily substances can pass from the blood into the brain across the blood-brain barrier; when it's higher, the barrier is "leakier." In 2014, Viorica Braniste, Sven Pettersson, and colleagues reported in *Science Translational Medicine* that germ-free mice had a leakier BBB than normal mice, starting before birth and lasting into adulthood. Their brain blood vessels had less of two tight junction proteins, occludin and claudin-5. When the team gave adult germ-free mice normal gut microbes, the barrier tightened. In follow-up experiments described in the full paper, giving germ-free mice a single butyrate-producing bacterium, or butyrate itself, also reduced leakage, and butyrate raised occludin levels in parts of the brain.

What about people? Here the evidence becomes thin. No study has shown that gut bacteria change BBB permeability in humans, and the microglia work has no direct human version. The closest human experiment tested SCFAs and stress hormones.

In a 2020 triple-blind trial, Dalile and colleagues gave 66 healthy men either a placebo or a supplement designed to release an SCFA mixture in the colon, for one week. Both SCFA doses reduced the rise in the stress hormone cortisol when the men faced a stressful public task, but they didn't change the men's mood ratings. That's one small, short study in men only, measuring a hormone rather than the brain directly. A 2019 review by the same group concluded that research on whether SCFAs explain microbial effects on mood and thinking is sparse, especially in humans. You'll learn much more about cortisol in Chapter 7.

A germ-free mouse is not a person who skipped vegetables



Germ-free mice have zero microbes from birth, which no human ever has. When you read "gut bacteria protect the blood-brain barrier," check whether the study compared mice with no microbes to mice with normal ones, because that's a big difference that doesn't translate directly to fiber on your plate.

Hype Meter: "Short-chain fatty acids protect the human blood-brain barrier"

Strong	Moderate	**Preliminary**	Hype

Verdict: Preliminary. In germ-free mice, the BBB is leakier and microglia are immature, and adding microbes or butyrate partly reverses this (Braniste 2014; Erny 2015). But no human study has shown that gut microbes or SCFAs change BBB permeability. The one small human trial of colon-delivered SCFAs (66 men, one week) found a lower cortisol response to stress, not a change in the brain barrier or mood.
What would change the grade: Human studies that measure BBB permeability directly (for example, with brain imaging) before and after changes in gut SCFAs, repeated in larger and more varied groups, would be needed to move it up. Animal research in general has a mixed record: only about one in three highly cited animal studies were later tested successfully in human trials.

Let's apply the six questions from Chapter 1 to the blood-brain barrier study, since it's the one behind many "your gut bacteria protect your brain" headlines.

How to read a gut-brain claim: the 2014 germ-free mouse BBB study

Question	This study
Mouse or human?	Mouse only. Germ-free mice were compared with mice that had normal microbes. No human data were collected.
Correlation or cause?	Closer to cause, in mice. The researchers changed the microbes (adding them to germ-free mice, or giving butyrate) and measured the barrier change. But germ-free mice differ from normal mice in many ways at once.
How many?	Small groups. One key adult experiment used 3 mice per group, which is common in this kind of lab work but limits confidence.
How long?	From before birth (embryonic days 13.5 to 18.5) to adulthood (8 to 10 weeks old), with recolonization experiments lasting days to weeks.
Who paid for it?	Public and nonprofit funders in Sweden, Singapore, the European Union, and the US, including the Swedish Research Council, the Swedish Brain Foundation, and the NIH, as listed in the paper.
Is something being sold?	No product. The paper states that the authors have no competing interests.

The conclusion: this is careful mouse work showing that, in mice, having microbes affects the BBB from early in life. It does **not** show that a particular food, supplement, or probiotic protects a person's brain barrier. A headline that skips from "germ-free mice" to "your brain" has jumped over the hardest part.

At the Bedside: The Leaky Gut Test

Meet the patient (fictional)

Tessa is a 15-year-old sophomore who spends a lot of time on social media. A wellness influencer she follows posted that bloating, tiredness, and "brain fog" are signs of leaky gut. Tessa bought an at-home "zonulin" test, which came back "high," and a "gut repair" powder. She also started eating much more fiber all at once. Now she's more bloated than before, has more gas, and is worried something is seriously wrong. Her mom brings her to her pediatrician.

What the doctor checks: The pediatrician asks about Tessa's symptoms, sleep, school stress, periods, family history of gut disease, and what she has been eating and taking. She asks about warning signs such as weight loss, blood in the stool, diarrhea that wakes her at night, or fevers; Tessa has none. The exam is normal. Because tiredness and bloating can have many causes, the doctor orders a few basic blood tests, including a blood count and a screening test for celiac disease. All are normal.

Connecting the signals: Tessa's symptoms got worse after she sharply increased her fiber. That fits normal fermentation: more fiber reaching the colon means more gas from microbes, which can cause bloating and cramps until the gut adjusts. The zonulin result doesn't change the picture. Research shows that widely used commercial zonulin tests detect other blood proteins, not zonulin, so a "high" result doesn't show that her gut is leaky.

Diagnosis: No sign of gut disease. Bloating and gas related to a fast increase in fiber. "Leaky gut syndrome" is not a recognized diagnosis, and her test result is not meaningful.

Why it happens: Fermentation by colon microbes makes short-chain fatty acids and gas (Section 6.3). Intestinal permeability is real and measurable in research, but consumer tests and the "leaky gut" label don't measure it reliably or explain everyday symptoms (Sections 6.7 and 6.8).

The mind-body side: Tessa has been checking her stomach constantly and reading about rare diseases at night, which keeps her anxious and makes her notice every gurgle. Worry about health can make normal body sensations feel louder and more alarming, a link you'll study in Chapter 8. The pediatrician takes Tessa's symptoms seriously, explains what the tests do and don't show, and suggests ways to step back from content that frightens her. If the worry keeps interfering with school or sleep, the care team can connect her with a counselor who works with health anxiety.

Treatment today: The main treatment is clear information and reassurance, along with a follow-up visit. The doctor recommends that Tessa talk with a registered dietitian about how to adjust her eating in a way that suits her, rather than making big changes based on social media. She asks Tessa to check with her before taking any supplement, since "gut repair" products are not tested or approved to treat any disease, and their contents can vary.

What's new in research: Researchers are trying to develop drugs that tighten the gut barrier. The most advanced, larazotide acetate, is an eight-amino-acid peptide thought to block zonulin signaling (Slifer and colleagues, 2021). It was tested in a phase 3 trial in adults with celiac disease, but the sponsor ended that trial in 2022, according to its ClinicalTrials.gov record (NCT03569007). It is not approved, and Odenwald and

Turner's 2017 review noted that no FDA-approved drugs targeted the gut barrier. **Evidence grade: Preliminary.** Barrier repair as a treatment for any disease remains unproven.

Your turn: reason through a variation

Tessa's friend Leo, also 15, has had diarrhea for three months, has lost weight without trying, and sometimes sees blood in his stool. His cousin says, "It's just leaky gut. Try the powder." How should you reason about this?

Answer: Leo's story is different. Weight loss, blood in the stool, and months of diarrhea are warning signs that need a doctor's evaluation, because they can point to conditions like inflammatory bowel disease, which you'll study in Chapter 9. Increased permeability does happen in Crohn's disease, but there it's a result of inflammation, and treating the inflammation is what matters. Calling it "leaky gut" and trying a powder could delay real diagnosis and care.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: All fiber is the same, so any fiber does the same thing in your gut.
Reality: Fiber is a family of different molecules. Soluble fibers form gels, insoluble fibers add bulk, and they differ in how easily microbes ferment them. Different fibers, and different microbes, produce different amounts of each short-chain fatty acid.

Myth: "Leaky gut" is a diagnosis doctors can confirm with a zonulin test.
Reality: Intestinal permeability is real and can be measured in research, mostly with sugar tests. But "leaky gut syndrome" isn't a recognized diagnosis, and two independent research teams found that common commercial zonulin kits measure other proteins instead.

Myth: The blood-brain barrier is a solid wall that nothing can cross.
Reality: The BBB is a selective filter made of sealed blood-vessel cells. Some substances, like the amino acid tryptophan and, according to animal research, SCFAs, cross with the help of transporter proteins. Others, like gut serotonin, don't.

Myth: If gut bacteria tighten the blood-brain barrier in mice, the same must be true in people.
Reality: The BBB and microglia results come from germ-free mice, which have no microbes at all. No human study has shown that gut bacteria change BBB permeability. Many results from mice don't hold up when tested in people.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Your brain fog is caused by a leaky gut. Toxins are leaking into your blood and crossing into your brain. My gut-sealing powder fixes both barriers in 30 days!"

Grade: Hype. Intestinal permeability is real, and the BBB is real, but this post chains together claims the evidence doesn't support. "Leaky gut syndrome" isn't a recognized diagnosis, no disease has been cured by fixing gut permeability, and no human study shows that gut changes alter the BBB. Someone is also selling a product with a promised timeline. A careful version would say: "The gut lining's permeability can change, and scientists are studying whether that matters for some diseases, but it isn't a proven cause of brain fog."

2. Predict: Riya's family switches from white rice to a mix of rice and lentils at most meals. Assuming her care team agrees with the change, what would you predict happens to fermentation in her colon over the next few weeks, and which SCFA would her colon lining use most?

More fermentable fiber would reach her colon, so her microbes would likely ferment more and make more short-chain fatty acids, along with more gas at first while her gut adjusts. Acetate would probably still be the most plentiful SCFA overall, but her colonocytes would take up and use butyrate most. How much changes depends on which microbes she has, and in Crohn's disease the inflamed or scarred parts of the gut can behave differently, which is why her care team should guide any change.

3. Explain: In the 1987 autopsy study, total SCFAs were about 375 micromoles per liter in the portal vein but only about 79 in peripheral blood. Explain the drop.

The portal vein carries blood directly from the gut to the liver, so it holds SCFAs fresh from the colon. On the way, the colon lining uses much of the butyrate, and then the liver takes up much of the propionate (and some acetate). By the time blood reaches the rest of the body, mostly acetate is left, at a much lower concentration.

4. Apply: A news story says, "Study finds mice without gut bacteria have leaky blood-brain barriers, so probiotics could protect your brain." Use the six questions to identify the two biggest problems.

First, mouse or human: the study is in mice, so it can't show what happens in people. Second, the comparison: germ-free mice have no microbes at all, while a person taking a probiotic already has trillions of microbes. The study tested having microbes versus having none, not adding one product to a normal gut. The headline also skips the question of whether the probiotic in question even makes the relevant molecules.

5. Read the data. In the 1987 study by Cummings and colleagues, researchers measured total SCFAs in intestinal contents from people who had died suddenly:

Location	Total SCFAs (mmol per kg of contents)	pH
End of small intestine (terminal ileum)	about 13	not reported here

Location	Total SCFAs (mmol per kg of contents)	pH
Cecum (start of colon)	about 131	about 5.6
Descending colon (later colon)	about 80	about 6.6

5. What does this data show, and what can't it show?

It shows that SCFAs are about ten times more concentrated at the start of the colon than at the end of the small intestine, and that they fall farther along the colon. That supports the idea that most fermentation happens in the first part of the colon, and the lower pH where SCFAs are highest fits acid build-up. It can't show what happens in living, healthy teens, since the samples came from adults after sudden death, and it can't show how diet changes these numbers, since diets weren't controlled. A helpful follow-up would measure SCFAs in living volunteers before and after a controlled change in fiber.

Exercises

Remember

1. Name the three main short-chain fatty acids and give the number of carbon atoms in each.

Answer

Acetate (2 carbons), propionate (3 carbons), and butyrate (4 carbons).

1. What is a colonocyte, and what is its main fuel according to the mouse research in this chapter?

Answer

A colonocyte is a cell that lines the inside of the colon. In mice, colonocytes use bacterial butyrate as their primary energy source.

Understand

1. Explain why dietary fiber reaches the colon while most starch from the same meal doesn't.

Answer

Human digestive enzymes break down most starch in the small intestine, where it's absorbed as sugar. We don't have enzymes that break down fiber, so it passes through the small intestine mostly intact and reaches the colon, where microbes can ferment it.

1. Explain the difference between how butyrate acts through a free fatty acid receptor and how it acts through gene regulation.

Answer

Through a receptor, butyrate binds a protein on the outside of a cell (like FFAR2) and triggers a signal inside, such as hormone release. Through gene regulation, butyrate enters the cell and blocks histone deacetylases, which leaves DNA more loosely wrapped and changes which genes are switched on.

Apply

1. Use the MicroSim to compare a fiber intake of 8 grams a day with 30 grams a day, at medium and at very low diversity. Record the fermentation and colonocyte fuel meters for all four combinations, then explain which change mattered more in the model and why the real answer might differ.
2. Sam reads that endurance exercise increases intestinal permeability and worries that cross-country is "giving him leaky gut." Using Section 6.7, write a short, accurate reply to Sam that explains what the research does and does not mean.

Analyze

1. Compare the evidence behind two statements: "Butyrate fuels colonocytes" and "SCFAs mature microglia." For each, identify whether the evidence comes from mice or humans, whether it shows cause or correlation, and which statement is closer to being true in people. Explain your reasoning.
2. The leaky gut claim combines several smaller claims. Break the claim "Leaky gut lets LPS into your blood, which causes depression" into at least three separate links, and analyze the evidence for each link using Sections 6.7 to 6.9.

Evaluate

1. A company sells an at-home zonulin test for teens "to check gut health." Evaluate whether the test is useful, citing at least two specific findings from this chapter, and decide what grade the product's claim deserves.

2. Some scientists argue that mouse studies of the BBB are valuable even though they don't prove anything about humans. Others say they create more hype than knowledge. Write a paragraph judging which view is more convincing, using the Braniste 2014 claim box as evidence.

Create

1. Design a study in human volunteers that could test whether a high-fiber diet changes intestinal permeability. Describe your groups, how long the study would last, what you would measure (and how), and one result that would support the hypothesis and one that wouldn't.
2. Create a short infographic script (five panels or fewer) that follows a lentil's fiber from Riya's grandmother's pot to the colon wall, labeling which steps are shown in humans and which only in mice.

Key Takeaways

- Dietary fiber is the part of plant foods that human enzymes can't digest. It reaches the colon, where microbes ferment it, mostly in the cecum and ascending colon.
- Fermentation produces gas and short-chain fatty acids, mainly acetate (usually the most abundant), propionate, and butyrate. In people, the colon lining takes up butyrate, the liver takes up propionate, and acetate reaches the rest of the body.
- In mice, butyrate is the main fuel for colonocytes and helps build calming regulatory T cells. SCFAs signal through free fatty acid receptors (FFAR2 and FFAR3) and, especially butyrate, by blocking histone deacetylases to change gene activity.
- Intestinal permeability is real and measurable, for example with sugar tests, and it rises with things like endurance exercise, NSAIDs, and gut inflammation. Most human data are correlative.
- "Leaky gut syndrome" is not a recognized diagnosis, commercial zonulin tests don't reliably measure zonulin, and no disease has been cured by fixing permeability.
- In mice, LPS from gut bacteria rises in the blood on a high-fat diet (metabolic endotoxemia) and can drive inflammation; human evidence is still developing.
- In germ-free mice, microglia stay immature and the blood-brain barrier is leakier; microbes and SCFAs partly reverse this. No human study has shown the same, so this remains Preliminary.

You followed fiber all the way!



You traced a lentil from the pot to the colon wall and learned to stop exactly where the human evidence stops. Next, in Chapter 7, we'll see what happens when stress hormones like cortisol enter the conversation, and why Sam's stomach knows when a big race is coming.

Quiz: Fiber, Fatty Acids, and the Blood-Brain Barrier

Test your understanding of Chapter 6. Choose the best answer, then click **Show Answer** to check.

Question 1

Which short-chain fatty acid is usually the most abundant, in both the colon and the blood?

A. Acetate

B. Butyrate

C. Propionate

D. Lactate

Show Answer

The correct answer is **A**. In the 1987 human study by Cummings and colleagues, acetate was the main SCFA in every sample, from colon contents to peripheral blood. Butyrate (B) gets a lot of attention, but most of it is used up by the colon lining, so much less of it reaches the blood.

Concept Tested: Acetate **Bloom's Level:** Remember

Question 2

Where in the human digestive tract does most fiber fermentation take place?

A. In the stomach, where acid breaks fiber apart

B. Throughout the small intestine, evenly from start to end

C. In the first part of the colon, the cecum and ascending colon

D. Only in the rectum, just before stool leaves the body

Show Answer

The correct answer is **C**. SCFA levels were low at the end of the small intestine and highest in the cecum, so most fermentation happens at the start of the colon. Option B is a common mix-up: the small intestine absorbs most digestible food, but fiber passes through it largely intact.

Concept Tested: Fermentation **Bloom's Level:** Remember

Question 3

What is a colonocyte?

A. A type of bacterium that ferments fiber in the colon

B. An epithelial cell that lines the inside of the colon

C. An immune cell in the brain that responds to SCFAs

D. A hormone released when fiber reaches the colon

Show Answer

The correct answer is **B**. Colonocytes are the cells lining the colon, and in mice they use bacterial butyrate as their primary fuel. Option A confuses the cell that uses butyrate with the microbes that make it.

Concept Tested: Colonocyte **Bloom's Level:** Remember

Question 4

In the 1987 autopsy study, total SCFAs fell from about 375 micromoles per liter in the portal vein to about 79 in peripheral blood. What best explains this drop?

A. SCFAs break down on their own within seconds of leaving the colon.

B. The kidneys filter SCFAs out before blood reaches the liver.

C. The blood-brain barrier absorbs most SCFAs from the blood.

D. The colon lining uses much of the butyrate and the liver takes up much of the propionate, so less is left for the rest of the body.

Show Answer

The correct answer is **D**. The changing mix of SCFAs from colon to portal blood to hepatic vein showed greater uptake of butyrate by the colon lining and propionate by the liver. Option C is wrong because the brain receives only a small share of blood SCFAs; the big drops happen in the gut wall and liver.

Concept Tested: Short-Chain Fatty Acid **Bloom's Level:** Understand

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Question 5

How does butyrate change which genes a cell switches on?

A. It cuts DNA at specific genes, like a pair of scissors.

B. It blocks histone deacetylases, leaving DNA more loosely wrapped and some genes easier to switch on.

C. It replaces the cell's DNA with bacterial genes.

D. It binds to the outside of the cell and stays there, never entering.

Show Answer

The correct answer is **B**. By blocking HDACs, butyrate leaves more acetyl tags on histones, loosening the DNA so some genes are easier to read. In mice, this happened at the *Foxp3* gene that makes T cells become regulatory T cells. Option D describes receptor signaling, which is a separate way SCFAs act.

Concept Tested: Gene Regulation by Butyrate **Bloom's Level:** Understand

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Question 6

Why do scientists say a "high" result on a common commercial zonulin blood test does not show that someone has a leaky gut?

A. Independent studies found that widely used kits detect other blood proteins, not zonulin itself.

B. Zonulin is only found in mice, so it can't be measured in people.

C. Zonulin levels are always high in healthy people.

D. The test measures stomach acid instead of blood proteins.

Show Answer

The correct answer is **A**. Scheffler and colleagues (2018) and Ajamian and colleagues (2019) found that commercial kits picked up proteins like properdin, haptoglobin, and complement C3 instead of zonulin. Option B is wrong: zonulin is studied in people, but the popular tests don't measure it reliably.

Concept Tested: Zonulin **Bloom's Level:** Understand

Question 7

Sam runs a hard 10-mile training run, and the next day a research team measures his small intestine permeability with a sugar test. Based on this chapter, what result is most likely, and what does it mean?

A. Permeability will be zero, because exercise seals tight junctions completely.

B. Permeability will be higher, which proves he has leaky gut syndrome and needs a supplement.

C. The sugar test can't be used on athletes.

D. Permeability may be higher than usual, but this is a normal response to endurance exercise, not a disease.

Show Answer

The correct answer is **D**. Camilleri's review lists endurance exercise as one of several stressors that increase intestinal permeability in people. Option B makes the leap the chapter warns against: a raised measurement isn't a diagnosis, and "leaky gut syndrome" isn't a recognized condition.

Concept Tested: Intestinal Permeability **Bloom's Level:** Apply

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Question 8

A student uses the Fiber to Butyrate MicroSim. At 30 grams of fiber a day with very low microbe diversity, the colonocyte fuel meter is lower than at 20 grams with high diversity. Which real-world idea is the model illustrating?

A. Fiber has no effect on SCFA production.

B. Only the amount of fiber matters; microbes are all the same.

C. How much butyrate is made depends on both the fiber eaten and which microbes are present to ferment it.

D. High microbe diversity causes the blood-brain barrier to tighten in people.

Show Answer

The correct answer is **C**. Fermentation needs both the fiber and the microbes that can ferment it, which is why the same meal can produce different amounts of SCFAs in different people. Option D is wrong because the blood-brain barrier effect has been shown only in germ-free mice, and the sim labels it that way.

Concept Tested: Butyrate **Bloom's Level:** Apply

Question 9

A headline says, "Gut bacteria keep your brain's barrier sealed." It is based on Braniste and colleagues (2014). Which statement best analyzes the gap between the study and the headline?

A. The study compared germ-free mice with normal mice, so it can't show what happens in people, who always have microbes.

B. The study was done in people, so the headline is accurate.

C. The study found no difference between germ-free and normal mice.

D. The study proved that a specific probiotic seals the human blood-brain barrier.

Show Answer

The correct answer is **A**. The study found a leakier BBB in germ-free mice and tighter barriers after adding microbes, but no human data were collected, and the comparison was between no microbes and normal microbes. Option D overstates it: no probiotic product was tested in people.

Concept Tested: BBB Permeability **Bloom's Level:** Analyze

Question 10

Cani and colleagues (2007) found that a high-fat diet raised blood LPS two to three times in mice, which they called metabolic endotoxemia. A wellness site says, "This proves fatty food leaks bacterial toxins into your blood and makes you sick." What is the strongest criticism of this claim?

A. LPS is not made by bacteria, so the study was mislabeled.

B. The study was in mice, and human studies on blood LPS are mostly observational, so it doesn't prove the same effect in people.

C. The study found that LPS lowers inflammation.

D. Metabolic endotoxemia means a large, deadly LPS level, which the mice did not have.

Show Answer

The correct answer is **B**. The 2007 findings are strong mouse evidence, but human links between diet, blood LPS, and health are mostly correlations that can't show which came first. Option D gets the definition backward: metabolic endotoxemia means a small, chronic rise in LPS, not a severe infection-level spike.

Concept Tested: Metabolic Endotoxemia **Bloom's Level:** Analyze

Chapter 7: Stress and the Gut

Summary

Stress reaches the gut through two systems: the fast fight-or-flight response and the slower hormonal chain called the HPA axis, in which the hypothalamus, pituitary gland, and adrenal glands pass signals down to release cortisol. Cortisol then switches the system off through negative feedback, which works well after short stress but can be overwhelmed by stress that keeps coming back. This chapter shows how stress hormones speed up the colon, activate mast cells, and make the gut lining more permeable in small human experiments, why those symptoms are real rather than "all in your head," and why stress can be linked to flares of Crohn's disease without causing it. It ends with germ-free mice, which revealed that gut microbes help set the stress system early in life, at least in mice.

Concepts Covered

1. Stress Response
2. Fight-or-Flight Response
3. Hypothalamus
4. Pituitary Gland
5. Adrenal Gland
6. HPA Axis
7. Corticotropin-Releasing Hormone
8. ACTH
9. Cortisol
10. Negative Feedback
11. Acute Stress
12. Chronic Stress
13. Stress and Gut Motility
14. Mast Cell
15. Early-Life Stress
16. Germ-Free Stress Response

Prerequisites

- Chapter 1: The Brain in Your Belly (the autonomic nervous system and gut motility)
- Chapter 3: Meet the Microbiome (germ-free mice, correlation vs causation)
- Chapter 4: The Immune System as a Sense Organ (cytokines, inflammation, the gut barrier)
- Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier (intestinal permeability)

Why stress shows up in your stomach



Almost everyone has felt their stomach react before a test, a game, or a hard conversation. This chapter explains which signals carry stress down to your gut, why those feelings are real body events and not "just nerves," and what that means for people living with IBS or IBD. As the nerve that runs between the brainstem and the gut, I have a front-row seat for this one.

7.1 Sam's Stomach Before the State Meet

It's the morning of the state cross-country championship, and Sam has been awake since 4:30. He ate half a bagel and gave up. By the time the team bus pulls into the course parking lot, his stomach is cramping, and he has already made two trips to the portable toilets. His coach jokes that it's "just nerves." Sam knows the joke is partly true, but it doesn't feel like nothing. His gut is doing something real. (Sam is a fictional student who appears throughout this book. He has IBS with mixed bowel habits, and his symptoms often get worse before big races and tests.)

Riya, his best friend, is there to cheer. She has her own question about stress. When she was diagnosed with Crohn's disease at 14, a relative said, "You've been so stressed with school. That's probably what did it." Riya has wondered ever since whether she gave herself Crohn's by worrying too much. (Riya is also a fictional student who appears throughout this book.)

By the end of this chapter, you'll be able to answer both of them: why stress goes straight to Sam's gut, and why the evidence doesn't support blaming stress for Riya's Crohn's disease, even though stress may affect her symptoms.

7.2 What Is Stress, Biologically?

Think about how a town handles an emergency. When the fire alarm rings, the first thing that happens is fast: sirens, trucks, people running. That lasts minutes. Then a slower response begins: the town redirects money, staff, and supplies to deal with the problem over hours or days. When the fire is out, someone has to call off the response, or the town wastes resources and wears out its crews.

Your body's stress system works the same way, with a fast branch, a slower branch, and an off switch. The **stress response** is the set of changes in the brain, nerves, hormones, and immune system that helps the body deal with a challenge, real or perceived, and then return to balance. The open textbook *Anatomy and Physiology 2e* (OpenStax) points out that stress can be physical, like an injury or being out in the cold without a coat, or psychological, like a fight with a loved one or a bad day at school. The body uses many of the same systems for both.

The stress response is a survival tool, and it is doing its job. Your brain can't tell the difference between a predator and a state championship as well as you might hope, so it gets the body ready for action in both cases. Some of what it does to get ready, like pulling resources away from digestion, explains a lot of what Sam feels.

For a deeper look at how the brain's emotion circuits trigger stress, see From Neuron to Bedside, Chapter 11.

7.3 The Fast Lane: Fight-or-Flight

The **fight-or-flight response** is the fast, nerve-driven part of the stress response, in which the sympathetic nervous system and the hormones epinephrine (adrenaline) and norepinephrine prepare the body for sudden physical effort within seconds. OpenStax describes the pathway: in response to danger or stress, a nerve route that begins in the hypothalamus signals the inner part of the adrenal glands to release epinephrine and norepinephrine into the blood. Those hormones raise heart rate and blood pressure, open the airways, and make the liver and muscles break down stored sugar for fuel.

Meanwhile, the body treats digestion as something that can wait. OpenStax notes that the same response narrows blood vessels that supply the digestive tract, and can cause a dry mouth and loss of appetite. Its chapter on the digestive system adds that, in general, sympathetic activation holds back the gut's own neurons (the enteric nervous system from Chapter 1), decreasing gut secretions and movement. That's part of why Sam couldn't finish his bagel.

So if fight-or-flight *slows* the gut, why does Sam need the bathroom? Stress also works through a second, slower system that acts differently on different parts of the gut. Its signals can push the colon to speed up even while the upper gut is being held back. To understand that, we need the HPA axis.

7.4 The Slow Lane: The HPA Axis

The slower branch of the stress response is a chain of three glands, each telling the next one what to do, a bit like a relay race where each runner hands off the baton.

The **hypothalamus** is a small region at the base of the brain that links the nervous system to the hormone system and helps control body temperature, hunger, thirst, sleep, and the stress response. The **pituitary gland** is a pea-sized gland hanging just below the hypothalamus that releases hormones controlling many other glands; its front part (the anterior pituitary) is the one involved here. Each **adrenal gland** is a small gland that

sits on top of a kidney, with an outer layer (the cortex) that makes steroid hormones like cortisol and an inner part (the medulla) that makes epinephrine and norepinephrine.

Together, these three form the **HPA axis**, short for hypothalamic-pituitary-adrenal axis: the hormone chain in which the hypothalamus signals the pituitary, the pituitary signals the adrenal glands, and the adrenal glands release cortisol. A 2006 review by Smith and Vale in *Dialogues in Clinical Neuroscience* calls the hormone at the top of this chain central to the stress response. It starts a cascade that ends with stress hormones pouring out of the adrenal cortex.

Here are the three relay runners:

1. **Corticotropin-releasing hormone** (CRH) is a hormone made by neurons in the hypothalamus that tells the pituitary to release ACTH. You'll also see it called corticotropin-releasing factor (CRF). They are two names for the same molecule; this book uses CRH, except when quoting research that uses CRF. CRH is also made outside the HPA axis, including in the gut wall, which becomes important in Section 7.8.
2. **ACTH** (adrenocorticotropic hormone) is a hormone released by the anterior pituitary into the blood that travels to the adrenal glands and tells their outer layer to make cortisol.
3. **Cortisol** is the main stress hormone in humans, a steroid made by the adrenal cortex that helps the body handle longer-lasting stress by raising available fuel and calming inflammation, and that shuts down its own production through feedback.

Step	Where	Hormone released	What it tells the next step
1	Hypothalamus (brain)	CRH	"Pituitary, release ACTH"
2	Anterior pituitary (below the brain)	ACTH	"Adrenal cortex, make cortisol"
3	Adrenal cortex (on the kidneys)	Cortisol	Acts on almost every tissue, and tells steps 1 and 2 to slow down

The fast lane and the slow lane differ mainly in speed and duration. OpenStax describes the adrenal medulla's hormones as the response to acute, short-term stress, and cortisol from the adrenal cortex as the response to longer-term stress. Both start in the hypothalamus, so a single stressful thought can switch on both.

7.5 Cortisol: Not the Villain

Cortisol has a bad reputation online, where it's often called "the stress hormone" as if it were poison. MedlinePlus, the US National Library of Medicine's health site, says cortisol affects almost every organ and tissue and helps your body respond to stress, reduce inflammation, control blood sugar and metabolism, and control blood pressure. Too much *or* too little cortisol can be very serious.

Cortisol also follows a daily rhythm. According to MedlinePlus, cortisol levels are normally highest in the morning and much lower by around 4 in the afternoon, which is why doctors who test cortisol in the blood often take samples at two different times. A morning rise in cortisol is part of how your body gets going each day, not a sign that something is wrong.

One of cortisol's jobs is especially relevant to this book. OpenStax explains that cortisol turns down parts of the immune system, which inhibits inflammation. That's the reason doctors use medicines that copy cortisol's effects, called glucocorticoids or corticosteroids, such as prednisone tablets, steroid inhalers, and hydrocortisone creams. The course of steroid medicine Riya took when she was diagnosed with Crohn's disease belongs to this family of drugs. Doctors decide when and how to use these medicines, because taking them for a long time has serious side effects, and stopping them suddenly can also be dangerous. That's a decision for a patient and their care team, never something to change on your own.

A hormone with a job, not a toxin



I like to think of cortisol as the long-shift worker of the stress response: it keeps fuel available, calms inflammation, and then helps shut the whole system down. The problems come when the shift never ends, not from cortisol existing.

7.6 Negative Feedback: The Stress System's Off Switch

A thermostat is the classic example of a system that controls itself. When the room gets warm enough, the thermostat turns the heater off. When it cools down, the heater turns back on. The output (heat) shuts down the thing that produces it.

Negative feedback is a control loop in which the product of a process acts back on the process to slow or stop it, keeping a body system near a set level. Cortisol is a textbook case. When cortisol rises in the blood, it acts on the hypothalamus and the pituitary, telling them to release less CRH and ACTH. Less ACTH means less cortisol. Smith and Vale write that this glucocorticoid feedback plays a prominent role in controlling how large the stress response gets and how long it lasts.

Why does this matter for the gut? Because many of stress's gut effects follow CRH, and cortisol feedback is what turns CRH back down. If feedback works well, a stressful morning becomes a calm afternoon, and the gut settles down too. If the stressor keeps returning before the system resets, the off switch is always one step behind. The brain also has other controls on the HPA axis; Smith and Vale describe inputs from emotion-related brain regions, the midbrain, and the brainstem that can push the hypothalamus up or down. So feedback is the main off switch, but not the only dial.

7.7 Acute Stress Versus Chronic Stress

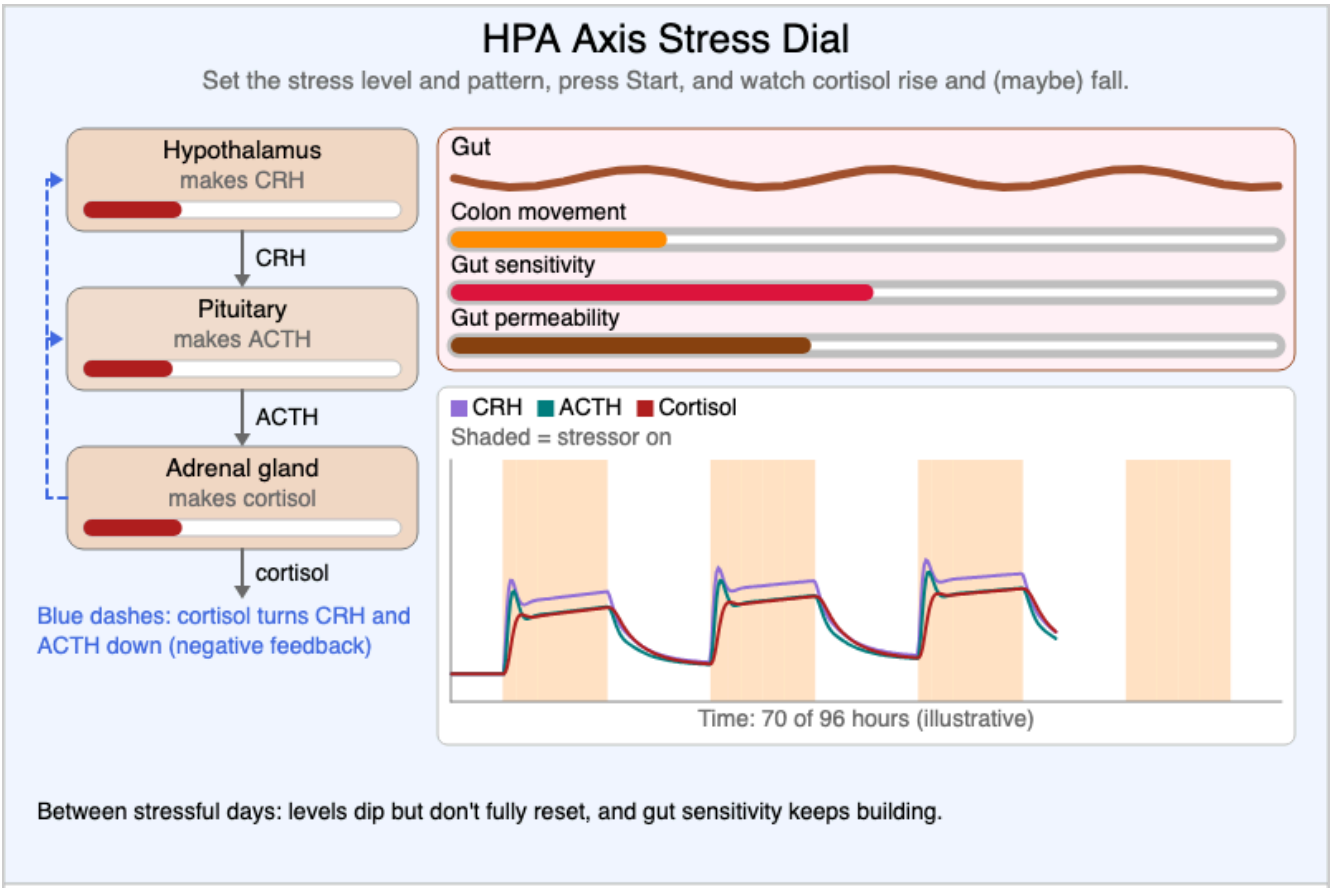
Not all stress is the same. The main difference that matters for the body is how long it lasts and how often it comes back.

Acute stress is short-term stress from a single challenge, such as a race, an exam, or a near-miss on a bike, in which the stress response switches on and then returns to baseline within minutes to hours once the challenge ends. **Chronic stress** is stress that lasts for weeks or months, or that keeps returning before the body has recovered, such as ongoing family conflict, money problems, bullying, or a long illness, so the stress systems stay switched on or are repeatedly reactivated.

OpenStax describes a classic model of the body's response to long-term stress, the general adaptation syndrome. The first stage, the alarm reaction, is the fight-or-flight response. If stress continues, the body moves to a resistance stage and tries to adapt. If stress lasts much longer, the stage of exhaustion can bring problems such as fatigue, depression, and a weakened immune response, which OpenStax links mainly to cortisol and the HPA axis. The model is a simplification, but it gets one thing right: short stress and long stress are not the same problem.

Acute stress is normal and often useful. A burst of cortisol and adrenaline helps get the body ready for effort, like a race. The worries about health come mostly from chronic stress, when the system rarely gets to rest. Use the MicroSim below to see the difference.

Diagram: HPA Axis Stress Dial



[Back to HPA Axis Stress Dial Lesson Plan]

Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch07-hpa-stress-dial/main.html

Open the HPA Axis Stress Dial fullscreen

MicroSim specification: HPA Axis Stress Dial

Type: microsim **sim-id:** ch07-hpa-stress-dial
Library: p5.js
Status: Implemented
Bloom Level: Understand
Bloom Verb: explain
Learning Objective: The learner will explain how cortisol's negative feedback returns the HPA axis to baseline after acute stress but not during repeated (chronic) stress, and describe the gut changes that accompany stress signaling.

Canvas: 530 px drawing area plus 120 px controls (iframe 652 px); responsive to about 380 px wide.

Controls: Start/Pause, Reset, Cortisol feedback on (checkbox, default on); Stress level slider (0 to 10, step 1, default 6); Pattern select (One stressful event, acute: a 2-hour stressor at hour 6; Stress every day, chronic: 12 stressful hours each day). One run lasts 96 illustrative hours.

Rules: A brain stress signal rises quickly while the stressor is on and fades over a few hours after it ends. CRH follows the brain signal, ACTH follows CRH, and cortisol follows ACTH, each with a short delay. With feedback on, cortisol above baseline lowers CRH and ACTH. Repeated stress slowly builds a background load that raises CRH and weakens feedback, so levels don't fully reset between stressful days. Colon movement follows CRH quickly; mast cell activation follows CRH but builds and fades slowly. Gut sensitivity and gut permeability are driven by mast cell activation plus CRH, not by cortisol directly. All values are relative and illustrative.

Feedback: Gland boxes turn from green to red as their hormone rises; a graph plots CRH, ACTH, and cortisol with the stressor shaded; a status line explains what is happening (stressor on, resetting after acute stress, not fully resetting with chronic stress, feedback off).

Provenance: Sections 7.4 to 7.9 (Smith and Vale 2006; OpenStax A&P 17.6; Taché and Million 2015; Fukudo 1998; Barbara 2004; Vanuytsel 2014). All model numbers are illustrative.

Start with the default, **One stressful event (acute)**, and press Start. Watch the order: CRH rises first, then ACTH, then cortisol, and the colon in the gut panel speeds up while the stressor (shaded) is on. Then notice what happens after the stressor ends. Rising cortisol pushes CRH and ACTH back down, and within a few hours everything returns to rest. Now uncheck **Cortisol feedback on** and run the same event again. The peak is higher and the return is slower, because nothing is actively turning the system off.

Next, turn feedback back on and choose **Stress every day (chronic)**. Watch the gut sensitivity meter over several days. Each stressful day sets off the same chain, but the levels between days don't fully reset, and the sensitivity meter keeps creeping up, because in the model mast cell activation builds faster than it fades. Try stress levels of 3 and 9 to see how intensity and repetition combine.

What this model leaves out

- Real cortisol has a daily rhythm (highest in the morning), which the model ignores; its resting level is flat.
- Chronic stress changes the HPA axis in complicated ways. In some people cortisol stays high, while in others the response becomes blunted. The model's single "load" variable is a teaching simplification.
- The fight-or-flight branch (epinephrine and norepinephrine) is left out, along with sleep, food, exercise, and individual differences in how people perceive stress.
- The gut effects are shown as three meters, and in the model, permeability is driven by CRH and mast cells, not by cortisol. That follows the 2014 human study in Section 7.9, where cortisol marked who was truly stressed but a mast cell blocker stopped the effect. In reality, gut effects differ by gut region, by person, and by condition, and most of the mechanisms come from animal studies and small human experiments.
- Times and levels are made-up teaching numbers, not measurements.

7.8 Stress and Gut Motility

Back to Sam's mystery: if fight-or-flight slows digestion, why does stress send him to the bathroom? Part of the answer is CRH.

Stress and gut motility describes how stress signals change the speed and pattern of muscle contractions in the digestive tract; in animal studies and small human experiments, stress hormones such as CRH speed up movement in the colon. A 2015 review by Taché and Million explains that CRH (they call it CRF) and its receptors are found in both the brain and the colon. In animal experiments, switching on one type of CRH receptor, called CRF1, in either place reproduced key features of IBS with diarrhea: faster colon movement, more bowel movements, watery stool, and increased pain sensitivity. Drugs that block CRF1 reduced these effects in animals.

Does this happen in people? A small study by Fukudo and colleagues in 1998 tested it directly. They gave CRH by injection to 10 people with IBS and 10 healthy volunteers while measuring pressure waves in their intestines. CRH increased movement in the descending colon (the part that runs down the left side of the belly toward the rectum) in both groups, and the increase was larger in the people with IBS. The IBS group also had a bigger ACTH response and abdominal symptoms that lasted longer. That's a small, short experiment, but it shows the same hormone acting on the human colon, and it hints that the system is more reactive in some people with IBS.

What about a pill that blocks CRH for IBS? Taché and Million note that, so far, the promising animal data have not turned into treatments: no CRF1-blocking drug is used to treat IBS. This is a good example of why the Hype Meter asks, "Mouse or human?"

Two systems, two directions



Here's how I keep it straight: fight-or-flight tends to slow the upper gut (goodbye, appetite), while CRH signaling can speed up the colon (hello, bathroom). Both can happen in the same stressful morning, which is exactly what Sam felt.

7.9 Mast Cells: Where Stress Meets the Gut's Immune System

The gut wall is full of immune cells, and one type sits right at the meeting point of stress, nerves, and the gut barrier. A **mast cell** is an immune cell that lives in tissues, including the gut lining, and stores chemical signals such as histamine and an enzyme called tryptase in small packets that it can release quickly, causing inflammation, changing nerve signaling, and loosening the barrier. You may know mast cells from allergies, where they help cause symptoms like itching and swelling.

In 2004, Barbara and colleagues looked closely at colon tissue samples from 44 people with IBS and compared them with healthy controls. In 34 of the 44 (77%), mast cells took up more of the colon lining than in controls. The IBS samples also released more histamine and tryptase. Mast cells within 5 micrometers of a nerve fiber (very close) were also more common in IBS, and only those close-to-nerve mast cells were linked to how severe and frequent people's abdominal pain was. That's a correlation, not proof of cause, but it suggests one way the immune system could make gut nerves more sensitive. You'll explore that idea in Chapter 8.

Stress connects to mast cells, too. In 2014, Vanuytsel and colleagues ran two experiments in healthy volunteers. In the first, 23 people went through several conditions, including giving a public speech, a well-known way to cause stress in a lab. Then they drank a sugar solution to measure how permeable their small intestine was (the lactulose-mannitol test from Chapter 6). Public speaking made the small intestine more permeable, but only in people whose cortisol rose, meaning those who were truly stressed. Here, cortisol worked as a sign of how stressed someone was, not as the proven cause of the change.

In the second experiment, with 13 volunteers, an injection of CRH copied the effect, and a drug that keeps mast cells from releasing their contents (a mast cell stabilizer) blocked both the CRH effect and the public-speech effect.

Put together, these studies sketch a pathway that runs through CRH and mast cells rather than through cortisol: stress raises CRH, CRH activates mast cells, and mast cells make the gut lining more permeable and possibly make nearby nerves more sensitive. Each link has some human evidence, but the studies are small, and the full chain hasn't been proven in one group of people.

Hype Meter: "Stress can physically change how your gut works"

Strong	**Moderate**	Preliminary	Hype

Verdict: Moderate. Small human experiments show that CRH speeds up the colon (10 people with IBS and 10 controls; Fukudo 1998) and that public-speaking stress raises small-intestine permeability in people whose cortisol rises (23 and 13 volunteers; Vanuytsel 2014). Mast cells near nerves are linked with pain in IBS (44 patients; Barbara 2004), and animal studies fill in the mechanisms. What's still unclear is how big these effects are in everyday life and how much they explain symptoms in each person. **What would change the grade:** Larger human studies that repeat these findings, especially ones that follow people through real-life stress like exam weeks and measure gut function directly, would move this toward Strong.

7.10 Did Stress Cause Riya's Crohn's Disease?

Now for Riya's question. It's one of the most common things people with IBD hear, and it can carry a lot of guilt.

Start with what's known about causes. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) says that doctors aren't sure what causes Crohn's disease. It lists an abnormal immune reaction against bacteria in the intestines, genes (Crohn's can run in families), environmental factors such as smoking, and differences in gut microbes. Stress is not on that list. You'll study these causes in detail in Chapter 9.

Stress does seem to matter for **flares**, the periods when symptoms come back. In a 2010 study from Manitoba, Canada, Bernstein and colleagues followed 704 people with IBD from a population-based registry, surveying them every three months for a year about possible triggers: pain relievers called NSAIDs, antibiotics, infections, major life events, mood, and perceived stress. Flares were identified with a validated symptom questionnaire, not with scopes or blood tests for inflammation. When they compared 174 people who had a flare with 209 who didn't, high perceived stress was the only factor that remained linked to flares in their final analysis, with about 2.4 times the odds of a flare. NSAIDs, antibiotics, and infections outside the gut were not linked in this study.

That's a meaningful finding, but notice what kind of evidence it is. It's an association in people, not an experiment. It's possible that stress triggers flares, that early, unnoticed inflammation makes people feel more stressed, or both. It also measured both stress and flares by questionnaire, so some "flares" may have been symptom changes without new inflammation. So the careful summary is: there's no good evidence that stress causes Crohn's disease, but higher stress is linked to more flares, and managing stress is a reasonable part of care.

That two-way possibility shows up beyond IBD. In a 12-year Australian study of more than 1,000 adults, Koloski and colleagues (2012) found that among people without a gut disorder at the start, higher anxiety predicted developing a functional gut disorder (such as IBS) later. And among people without high anxiety or

depression at the start, having a functional gut disorder predicted higher anxiety and depression 12 years later. The brain affects the gut, and the gut affects the brain.

Hype Meter: "Stress causes IBD"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. NIDDK lists immune, genetic, environmental, and microbial factors as possible causes of Crohn's disease, and stress isn't among them. The human evidence that does exist links stress to *flares* in people who already have IBD (704 people followed for a year; Bernstein 2010), which is a narrower and better-supported claim, worth about Moderate on its own. Blaming people for causing their IBD with stress is not supported and can be harmful. **What would change the grade:** A few large studies have looked forward in time. In one, about 150,000 US women in the Nurses' Health Study who reported recent depressive symptoms were later diagnosed with Crohn's disease about 2.4 times as often (but not ulcerative colitis; Ananthakrishnan 2013). That's an association with low mood, not proof that stress causes IBD, and early, undiagnosed disease could explain part of it. If you have Crohn's disease and have felt down, this does not mean your feelings caused your illness. Repeated studies like this that measure stress itself, account for genes, smoking, and early symptoms, and find the same result in different groups would be needed to move "stress causes IBD" up to Preliminary.

If you're going through this

If someone has told you that stress caused your Crohn's disease, colitis, or IBS, please know that the evidence doesn't support blaming you. Stress can make symptoms worse, which means stress tools can be part of your care, alongside medicine, not instead of it. Ask your doctor about options like counseling or gut-directed therapies, and tell your care team if stress or worry is affecting your sleep, schoolwork, or mood.

Stress, worry, and low mood often travel together with gut conditions. Later chapters cover anxiety and depression in detail. If things feel heavy right now, you don't have to wait for a later chapter to get help.

If you are struggling right now

If you are thinking about suicide or are in crisis, call or text **988** to reach the 988 Suicide & Crisis Lifeline (in the US), or go to the nearest emergency room. Outside the US, you can find a helpline at findahelpline.com. You can also talk to a parent, school counselor, or doctor.

7.11 Early-Life Stress: Setting the Dial Young

Stress early in life seems to leave a longer mark. **Early-life stress** is serious or repeated stress experienced before birth, in infancy, or in childhood, such as separation from caregivers, neglect, or trauma, that may change how the stress system and the gut-brain axis respond later in life.

Much of the direct evidence comes from animals. In a 2009 study, O'Mahony and colleagues separated newborn male rat pups from their mothers for 3 hours a day from day 2 to day 12 after birth. As adults, these rats had higher levels of corticosterone (the main stress hormone in rodents), produced more fecal pellets when placed in a new, stressful situation, had more sensitive guts, showed a stronger immune response in a lab test, and had different gut microbes compared with rats that stayed with their mothers. The researchers proposed this as a model for studying IBS and depression.

In people, researchers have reported that difficult early-life experiences are associated with a higher chance of several conditions later, including depression and IBS, as the O'Mahony paper's background notes. Those human links are correlations: many other things that come with hard early experiences, like poverty or illness, could also play a role. And a hard early life does not doom anyone. The stress system can change throughout life, and support, safety, and treatment matter at every age.

For families

Stress-related gut symptoms are real, not attention-seeking or "just in their head," and saying so out loud helps. Phrases like "Just relax" or "You're making yourself sick" usually add pressure; "Your body is reacting to a lot right now, what would help?" works better. Before known stressful events, like exams or races, simple planning (bathroom access, a calm morning routine, extra time) can lower the load. If gut symptoms come with ongoing sadness, panic, or trouble at school, ask your child's doctor about support for both.

7.12 Microbes Train the Stress System: Germ-Free Mice

So far, the arrows have pointed from the brain to the gut. One famous experiment showed an arrow pointing the other way.

In 2004, Sudo and colleagues at Kyushu University in Japan compared germ-free mice (raised with no microbes, from Chapter 3) with mice that had normal gut microbes. They put both groups through a mild stressor, an hour of restraint in a small tube. The germ-free mice had a much bigger rise in ACTH and corticosterone than the normal mice. This exaggerated reaction is called the **germ-free stress response**: the larger-than-normal HPA axis response to stress seen in mice raised without any microbes, which suggests that gut microbes help tune the stress system as it develops.

The details are what made the study famous:

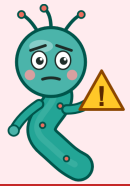
- The exaggerated response showed up with restraint stress but not with a different stressor (ether), so it wasn't a general malfunction.
- Giving germ-free mice one bacterial species, *Bifidobacterium infantis*, reversed the exaggerated response.

- Giving one harmful strain of *E. coli* made the response bigger.
- Giving germ-free mice feces from normal mice partly corrected the response, but only when it was given early in life. Given later, it didn't help.

That last point suggested a "window" during development when microbes help set the stress system. Other mouse research shows the arrow running in both directions: in 2011, Bailey and colleagues found that a social stressor changed the gut bacteria of mice, lowering one group (*Bacteroides*) and raising another (*Clostridium*), and that mice whose microbes had been reduced with antibiotics didn't show the usual stress-driven rise in the inflammatory signal IL-6. In mice, at least, stress shapes microbes and microbes shape the stress response.

What about people? The human evidence is much thinner. Remember the 2020 trial from Chapter 6: 66 healthy men given colon-delivered short-chain fatty acids, or SCFAs (molecules made by gut microbes), for one week had a smaller cortisol response to a stressful task than men given placebo. That's one small study, in men only, with no change in mood. A 2019 review by Cryan and colleagues in *Physiological Reviews* concludes that stress can affect the microbiota-gut-brain axis at every stage of life, while noting that much of the evidence comes from animal models.

Mice make corticosterone, people make cortisol



Watch for this slip in headlines: the main stress hormone in mice is corticosterone, not cortisol, so "germ-free mice had higher cortisol" is wrong. It's a small detail that tells you whether a writer actually read the study.

Hype Meter: "Your gut bacteria control your stress response"

Strong	Moderate	**Preliminary**	Hype

Verdict: Preliminary. In mice, the evidence is strong: germ-free mice have exaggerated stress-hormone responses, and early colonization with microbes partly prevents this (Sudo 2004), while stress itself changes mouse gut microbes (Bailey 2011). In humans, the evidence is limited to small, short trials such as one week of colon-delivered SCFAs in 66 healthy men, which lowered the cortisol response to stress (Dalile 2020). "Control" overstates even the mouse findings. **What would change the grade:** Larger randomized trials in people of different ages and sexes, showing that a specific microbial change reliably changes the stress-hormone response and how people feel, would move this toward Moderate.

Let's apply the six questions to the Sudo study, since it launched much of this field.

How to read a gut-brain claim: the 2004 germ-free mouse stress study

Question	This study
Mouse or human?	Mouse only. Germ-free, normal, and single-microbe mice were compared. The hormones measured were ACTH and corticosterone.
Correlation or cause?	Cause, in mice. The researchers changed which microbes the mice had and measured the stress response. Germ-free mice differ from normal mice in many ways, though, and people are never germ-free.
How many?	Moderate for a mouse study. The main time-course experiment used about 50 germ-free and 50 normal mice in total (6 to 11 per time point); other experiments used about 18 to 24 per group.
How long?	The stress test was 1 hour of restraint. Mice were tested as young adults, with some groups given microbes 1 or 3 weeks before testing.
Who paid for it?	A research grant from Japan's Ministry of Education, Culture, Sports, Science and Technology, and the Yakult Bioscience Research Foundation (Yakult is a company known for probiotic drinks).
Is something being sold?	No product was tested or sold in the study. The funding link to a probiotic company's foundation doesn't make the results wrong, but keep it in mind when people use this study to promote probiotics.

The conclusion: this experiment shows that, in mice, early microbes help tune the HPA axis. It does **not** show that a probiotic will lower a person's stress, and the timing result suggests that even in mice, adding microbes later in life didn't fix the response.

At the Bedside: Finals Week

Meet the patient (fictional)

Daniel is an 18-year-old college freshman who moved away from home in August. During midterms and again during his first finals week, he had cramping belly pain and urgent, loose stools several times a day, sometimes running out of exams to find a bathroom. His symptoms ease over winter break. Thinking back, he realizes he had milder versions of this during junior-year exams in high school. He's embarrassed, and he's started skipping study groups in case he needs to leave.

What the doctor checks: The campus health doctor takes a careful history: when symptoms happen, what stool looks like, whether pain improves after a bowel movement, and whether there are warning signs like blood in the stool, weight loss, fever, symptoms that wake him at night, or a family history of IBD or celiac disease. Daniel has none of these. His exam is normal, and basic blood and stool tests to look for anemia, inflammation, infection, and celiac disease all come back normal.

Connecting the signals: Daniel's symptoms track stress closely. During exams, his HPA axis and fight-or-flight systems are switched on. CRH signaling can speed up colon movement, and stress-related mast cell activation can increase gut permeability and may make gut nerves more sensitive, so normal gut activity is felt as pain and urgency. His history over more than two years, with pain linked to bowel movements and changes in stool, fits a pattern doctors recognize.

Diagnosis: Irritable bowel syndrome with predominant diarrhea (IBS-D), made using symptom-based criteria after tests ruled out other causes. Many published studies used the Rome IV criteria, and the newer Rome V criteria (published in 2026) are now the current version. You'll learn how these criteria work in Chapter 10.

Why it happens: IBS is a disorder of gut-brain interaction. In people with IBS, the colon can respond more strongly to CRH than in people without IBS (Section 7.8), and mast cells near gut nerves are linked with pain (Section 7.9). Stress doesn't create the condition out of nothing, but it turns up signals that are already more reactive.

The mind-body side: Daniel's worry about having symptoms during exams has become its own stressor, which feeds back into his gut, a loop that can keep symptoms going. The doctor makes clear that his symptoms are real and physical, not imagined. Together they talk about sleep, routines, and campus counseling services, and she explains that psychological treatments for IBS work on the gut-brain connection itself, not because the problem is "in his head."

Treatment today: Care for IBS usually starts with explanation and reassurance, a plan for exam days (for example, arranging bathroom access with the disability services office), and attention to sleep and regular meals. Depending on symptoms, the doctor may suggest diet changes with a dietitian, medicines for diarrhea or pain, or a referral for a brain-gut behavioral therapy such as cognitive behavioral therapy (CBT) or gut-directed hypnotherapy. Which options fit is a decision for Daniel and his care team.

What's new in research: In 2024, Goodoory and colleagues published a network meta-analysis in *Gastroenterology* combining 42 randomized trials with 5,220 participants. Several brain-gut behavioral therapies, including self-guided CBT, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy, may improve abdominal pain in adults with IBS, and none was better than another. **Evidence grade: Moderate.** No trial was at low risk of bias in every area, so the benefits may be somewhat overestimated, but the effect showed up across many trials.

Your turn: reason through a variation

Daniel's roommate, Marcus, also gets diarrhea during finals. But Marcus has also lost 10 pounds without trying since September, sometimes sees blood in his stool, and wakes up at night needing the bathroom. He says, "It's just stress, like Daniel." How would you reason about this?

Answer: Marcus has warning signs that stress alone doesn't explain: unplanned weight loss, blood in the stool, and nighttime symptoms. These need a doctor's evaluation for conditions like inflammatory bowel disease or infection. Stress can make many gut problems worse, but it's never safe to assume "it's just stress" when warning signs are present.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Stomach symptoms from stress are imaginary or "all in your head."
Reality: Stress hormones cause measurable changes in the gut. In small human studies, CRH sped up the colon and public-speaking stress made the small intestine more permeable. The brain and gut are connected by real nerves and hormones, so a stress-related symptom is a real body event.

Myth: Cortisol is purely bad, so less is always better.
Reality: Cortisol is essential. It helps control blood sugar and blood pressure, calms inflammation, and switches off the stress response through negative feedback. Too little cortisol is dangerous, just like too much. Problems come mostly from stress that never lets the system rest.

Myth: Stress causes inflammatory bowel disease.
Reality: Doctors aren't sure what causes Crohn's disease, but NIDDK lists immune, genetic, environmental, and microbial factors, not stress. In people who already have IBD, high perceived stress is linked to more flares, which is a different and narrower claim.

Myth: You can "detox" or "flush" cortisol with a special drink or supplement.
Reality: Your body already controls and clears cortisol on its own, mainly through negative feedback that lowers its production. Products that promise to "detox cortisol" are selling a solution to a problem described in a misleading way. If you're worried about stress or hormones, talk to a doctor.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Your bloating is high cortisol! Gut bacteria control your stress hormones, so our probiotic gummies lower cortisol and calm your gut in just one week."

Grade: Hype. The strongest evidence that microbes affect the stress response comes from germ-free mice, which make corticosterone, not cortisol, and have no microbes at all. In people, evidence is limited to small, short trials, such as one week of colon-delivered SCFAs in 66 men, which lowered the cortisol response to a stress test but didn't change mood. No study in this chapter tested these gummies, and bloating has many causes. A careful version would say: "In mice, gut microbes help set the stress system early in life; whether any product changes stress hormones in people is still being studied."

2. Predict: Sam has a big chemistry test on Friday and the state meet on Saturday. Using the HPA axis, predict what happens to his cortisol across the two days, and what might happen to his gut.

Each event should trigger the chain: CRH from the hypothalamus, ACTH from the pituitary, and cortisol from the adrenal glands. If the events are close together, cortisol from Friday may not fully settle before Saturday's stress starts again, so the system has less time to reset. In his gut, CRH signaling could speed up his colon and contribute to urgency, while fight-or-flight could reduce his appetite. Because he has IBS, his gut may react more strongly than a friend's.

3. Explain: In the MicroSim, turning off cortisol feedback makes the cortisol peak higher and the return slower after one stressful event. Explain why, using the idea of negative feedback.

Normally, rising cortisol acts on the hypothalamus and pituitary to reduce CRH and ACTH, which reduces further cortisol release. That limits how high cortisol climbs and helps it fall once the stressor ends. Without feedback, CRH and ACTH stay high for longer, so the adrenal glands keep making cortisol until the brain's stress signal fades on its own, which takes more time.

4. Apply: A news story reports, "Mice raised without germs panic more under stress, so kids should eat more dirt." Use what you know about the Sudo 2004 study to identify what the headline gets wrong.

The study measured stress hormones (ACTH and corticosterone), not "panic." It compared mice with no microbes at all to mice with normal microbes, which isn't like children who already have trillions of microbes. It also found that adding microbes later in life didn't fix the response, and that one harmful *E. coli* strain made the response worse, so "more germs" isn't automatically better. And it was in mice, so it can't tell us what children should eat.

5. Read the data. In the 2014 study by Vanuytsel and colleagues, healthy volunteers drank a sugar solution, and researchers measured the lactulose-to-mannitol ratio in their urine (a higher ratio means a more permeable small intestine). Here are average values from the paper's abstract:

Condition	Lactulose-mannitol ratio (average)
Control (first study, 23 volunteers)	0.030
Indomethacin, a pain reliever known to raise permeability (positive comparison)	0.071
Public speech (stress)	0.059
Control (second study, 13 volunteers)	0.028
CRH injection	0.042

5. What does this data show, and what can't it show?

It shows that public-speaking stress roughly doubled the ratio compared with control (0.059 vs 0.030), an effect in the same range as a drug known to raise permeability, and that CRH alone also raised it (0.042 vs 0.028). That supports the idea that stress and CRH can make the human small intestine more permeable, at least briefly. It can't show that this causes symptoms or disease, since the volunteers were healthy and the tests lasted hours. It also can't tell us about people in general, because the groups were small (23 and 13), and the speech effect appeared only in people whose cortisol rose. A helpful follow-up would repeat the test in a larger group, including people with IBS, and track symptoms during real-life stress.

Exercises

Remember

1. List the three parts of the HPA axis in order and name the hormone each one releases.

Answer

Hypothalamus (CRH), anterior pituitary gland (ACTH), adrenal cortex (cortisol).

1. What is a mast cell, and name one chemical it releases.

Answer

A mast cell is an immune cell that lives in tissues, including the gut lining, and stores chemical signals it can release quickly. Examples include histamine and tryptase.

Understand

1. Explain how negative feedback keeps a single stressful event from raising cortisol forever.

Answer

As cortisol rises, it acts on the hypothalamus and pituitary to reduce CRH and ACTH. With less ACTH, the adrenal glands make less cortisol, so once the stressor ends, cortisol falls back toward its resting level.

1. Explain why fight-or-flight can reduce appetite while stress can also cause diarrhea.

Answer

Fight-or-flight signals generally hold back the enteric nervous system and reduce gut secretions and movement, and they can reduce appetite. Separately, CRH signaling in the brain and colon can speed up colon movement. The two systems act on different parts of the gut at the same time.

Apply

1. Use the MicroSim to run one stressful event at stress levels 3, 6, and 9, with feedback on. Record the highest cortisol point on the graph (as a rough fraction of the graph's height) and the number of hours until it returns to rest. Describe the pattern, and explain why these numbers can't be compared to real cortisol measurements.
2. Riya's younger cousin, who has no gut condition, says she always needs the bathroom before swim meets and wonders if she has IBS. Using this chapter, explain what is probably happening and what would make a doctor consider IBS instead.

Analyze

1. Compare the Bernstein 2010 IBD flare study and the Sudo 2004 germ-free mouse study using four of the six questions. Which one tells you more about people, and which one is better at showing cause?
2. The Koloski 2012 study found that anxiety predicted later functional gut disorders and that gut disorders predicted later anxiety. Analyze why this two-way finding makes it hard to say "anxiety causes IBS" or "IBS causes anxiety," and suggest one kind of study that could help untangle it.

Evaluate

1. A wellness website says that because CRH speeds up the colon, "stress-blocking supplements" can cure IBS. Evaluate this claim using what Taché and Million (2015) reported about CRF1-blocking drugs, and assign a Hype Meter grade.
2. Some people argue that telling IBS patients "stress affects your gut" is unhelpful because it sounds like blame. Others say it is empowering because it opens up more treatment options. Judge which framing is better, and write two sentences a doctor could say that keep the science accurate without blaming the patient.

Create

1. Design a study that tests whether exam stress changes gut permeability in high school students with and without IBS. Describe your groups, when you would take measurements, what you'd measure (and how), and what ethical protections you'd need.
2. Create a one-page "exam day plan" for a student like Sam that uses at least three ideas from this chapter (for example, the timing of cortisol, the speed-up of the colon, and the role of worry), without giving any medical or medication advice.

Key Takeaways

- The stress response has a fast branch (fight-or-flight, driven by the sympathetic nervous system, epinephrine, and norepinephrine) and a slower branch (the HPA axis: hypothalamus, pituitary gland, and adrenal glands).
- In the HPA axis, CRH from the hypothalamus triggers ACTH from the pituitary, which triggers cortisol from the adrenal cortex. Cortisol is essential: it helps control blood sugar, blood pressure, and inflammation, and it follows a daily rhythm.
- Negative feedback lets cortisol shut down CRH and ACTH, so acute stress resolves. Chronic stress keeps reactivating the system before it can fully reset.
- Stress changes the gut in measurable ways. In small human studies, CRH sped up the colon, and public-speaking stress made the small intestine more permeable by a route that depended on mast cells; mast cells near nerves are linked to IBS pain. Stress-related gut symptoms are real.
- There's no good evidence that stress causes IBD, but high perceived stress is linked to more flares, and brain and gut affect each other in both directions over time.
- In animals, early-life stress has long-lasting effects on the stress system and the gut; in people, links between early adversity and conditions like IBS are associations.
- Germ-free mice show an exaggerated stress-hormone response that early colonization with microbes partly prevents. Human evidence that microbes shape the stress response is still Preliminary.

You mapped the stress highway!



You now know why Sam's stomach knows race day is coming, and why Riya didn't cause her Crohn's by worrying. Next, in Chapter 8, we'll follow those sensitized gut nerves to the brain and learn how the same signal can turn into more pain.

Quiz: Stress and the Gut

Test your understanding of Chapter 7. Choose the best answer, then click **Show Answer** to check.

Question 1

What is the correct order of hormones in the HPA axis?

A. Cortisol, then ACTH, then CRH

B. CRH, then ACTH, then cortisol

C. ACTH, then CRH, then cortisol

D. Epinephrine, then CRH, then ACTH

Show Answer

The correct answer is **B**. The hypothalamus releases CRH, which tells the anterior pituitary to release ACTH, which tells the adrenal cortex to make cortisol. Option A reverses the chain; cortisol comes last and then feeds back on the first two steps.

Concept Tested: HPA Axis **Bloom's Level:** Remember

Question 2

Which part of the body releases ACTH?

A. The adrenal medulla

B. The colon lining

C. The hypothalamus

D. The anterior pituitary gland

Show Answer

The correct answer is **D**. ACTH comes from the anterior pituitary and travels in the blood to the adrenal glands. The hypothalamus (C) is one step earlier: it releases CRH, which tells the pituitary to release ACTH.

Concept Tested: ACTH **Bloom's Level:** Remember

Question 3

What is a mast cell?

A. An immune cell in tissues, including the gut lining, that stores and quickly releases signals such as histamine and tryptase

B. A neuron in the hypothalamus that makes CRH

C. A hormone-making cell in the adrenal cortex

D. A gut bacterium that produces stress hormones

Show Answer

The correct answer is **A**. Mast cells sit in tissues like the gut lining and release stored chemicals that can cause inflammation, affect nerves, and loosen the barrier. Option D is a mix-up: mast cells are the body's own immune cells, not microbes.

Concept Tested: Mast Cell **Bloom's Level:** Remember

Question 4

Why does cortisol usually return to its resting level a few hours after a single stressful event ends?

A. Cortisol is broken down by gut bacteria as soon as it is made.

B. The adrenal glands run out of cortisol after one use.

C. Rising cortisol acts on the hypothalamus and pituitary to reduce CRH and ACTH, a process called negative feedback.

D. The fight-or-flight response destroys cortisol in the blood.

Show Answer

The correct answer is **C**. Cortisol turns down the very signals that cause its release, limiting how high and how long the response goes. Option B is a common misconception: the adrenal glands don't "run out"; the system is actively switched off.

Concept Tested: Negative Feedback **Bloom's Level:** Understand

Question 5

Fight-or-flight generally slows digestion. So why can stress cause urgent diarrhea?

A. CRH signaling in the brain and colon can speed up colon movement, even while the upper gut is held back.

B. Stress makes the stomach empty faster, which pushes food straight into the colon.

C. Diarrhea during stress is imagined; the gut doesn't actually change.

D. Cortisol directly dissolves stool in the colon.

Show Answer

The correct answer is **A**. In animals, activating CRF1 receptors in the brain or colon speeds colon movement and causes watery stool, and in a small human study, CRH increased colon movement. Option C is the "all in your head" myth; these are measurable changes in gut function.

Concept Tested: Stress and Gut Motility **Bloom's Level:** Understand

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Question 6

Which statement best explains the difference between acute and chronic stress?

A. Acute stress is always harmful, and chronic stress is always harmless.

B. Acute stress involves only cortisol, and chronic stress involves only adrenaline.

C. Acute stress happens only in adults, and chronic stress only in children.

D. Acute stress is a short challenge after which the system resets; chronic stress lasts or keeps returning before the system can fully recover.

Show Answer

The correct answer is **D**. The key difference is duration and repetition. A single race or exam triggers a response that negative feedback can shut down, while ongoing stress keeps reactivating the system. Option A gets it backward: short stress is normal and often useful.

Concept Tested: Chronic Stress **Bloom's Level:** Understand

Question 7

Riya asks Dr. Alvarez whether the stress of high school caused her Crohn's disease. Based on this chapter, which answer is most accurate?

A. "Yes, stress is the main known cause of Crohn's disease."

B. "Stress isn't a known cause of Crohn's, but in people who have IBD, high stress is linked to more flares."

C. "Stress has no connection at all to IBD symptoms."

D. "Only stress in early childhood can cause Crohn's disease."

Show Answer

The correct answer is **B**. NIDDK lists immune, genetic, environmental, and microbial factors, not stress, as possible causes, while a year-long study of 704 people with IBD linked high perceived stress to flares. Option C goes too far in the other direction: stress may affect symptoms even though it isn't a known cause of the disease.

Concept Tested: Stress Response **Bloom's Level:** Apply

Question 8

In the HPA Axis Stress Dial MicroSim, a student runs one stressful event with feedback on, then again with feedback off. What should she observe the second time?

A. Cortisol doesn't rise at all.

B. CRH rises after cortisol instead of before it.

C. The cortisol peak is higher and it takes longer to return to rest.

D. The gut panel stops moving completely.

Show Answer

The correct answer is **C**. Without feedback, nothing actively turns CRH and ACTH down when cortisol rises, so cortisol climbs higher and falls more slowly. Option A is wrong because the stressor still starts the CRH, ACTH, and cortisol chain; feedback controls the shutdown, not the start.

Concept Tested: Cortisol **Bloom's Level:** Apply

Question 9

Sudo and colleagues (2004) found that germ-free mice had a bigger ACTH and corticosterone response to restraint stress than normal mice. A blog writes, "Germ-free mice prove probiotics lower cortisol in people." What is the strongest analysis of this claim?

A. The claim is accurate because the study measured cortisol in people.

B. The claim is accurate because any bacteria lowered the stress response in the study.

C. The claim is wrong only because the study was too old.

D. The study was in mice (which make corticosterone, not cortisol), compared no microbes with normal microbes, and found later colonization didn't help, so it can't show what probiotics do in people.

Show Answer

The correct answer is **D**. The germ-free stress response is a mouse finding about having microbes versus none, with a timing window early in life. Option B is wrong because one harmful *E. coli* strain actually made the response bigger, so not all bacteria lowered it.

Concept Tested: Germ-Free Stress Response **Bloom's Level:** Analyze

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Question 10

O'Mahony and colleagues (2009) separated rat pups from their mothers for 3 hours a day and found lasting changes in stress hormones, gut sensitivity, and gut microbes. Studies in people link hard early-life experiences with later IBS. Why is the human link weaker evidence of cause than the rat study?

A. Human studies are observational, so other factors that come with early adversity, like poverty or illness, could explain the link.

B. Rats have no stress hormones, so the rat study shows nothing.

C. Human studies always use more people, which makes them less reliable.

D. Early-life stress has been proven to have no effect in people.

Show Answer

The correct answer is **A**. In the rat study, researchers assigned the stress and controlled other factors, so it can show cause in rats. Human studies can only observe who had hard early experiences, and many other differences could explain the link. Option D overstates the point: the human link is real as an association, just not proven as cause.

Concept Tested: Early-Life Stress **Bloom's Level:** Analyze

Chapter 8: Pain, Sensitivity, and the Gut

Summary

Gut pain is real, common, and strangely hard to describe. This chapter follows a pain signal from sensors in the gut wall, through the spinal cord, and up to the brain areas that turn it into an experience. Along the way you will see why gut pain is vague and often felt in the wrong place, how the spinal cord and brain can turn pain signals up or down, and why many people with IBS feel gut stretch as painful at lower levels than other people do. You will also learn why "the tests are normal" never means "the pain is imaginary," and which approaches help when the pain system itself is turned up too high.

Concepts Covered

1. Nociceptor
2. Somatic Pain
3. Visceral Pain
4. Referred Pain
5. Dorsal Root Ganglion
6. Dorsal Horn
7. Thalamus
8. Insula
9. Anterior Cingulate Cortex
10. Pain Perception
11. Gate Control Theory
12. Visceral Hypersensitivity
13. Peripheral Sensitization
14. Central Sensitization
15. Descending Pain Modulation
16. Balloon Distension Test
17. Pain Catastrophizing

Prerequisites

- Chapter 2: The Vagus Highway (afferent signals, spinal afferent nerves, interoception)
- Chapter 4: The Immune System as a Sense Organ (inflammation and cytokines)
- Chapter 7: Stress and the Gut (the stress response and mast cells)

Same signal, different pain



Belly pain is one of the most common reasons people see a doctor, and one of the most frustrating, because tests often come back normal. This chapter explains how pain is built from signals that can be turned up or down at several stops along the way. If anyone has ever told you your pain was "just in your head," you're about to see why that sentence gets the science wrong.

8.1 Same Gas, Different Pain

Imagine two students sitting side by side in an assembly. Both ate the same bean burrito, and both have about the same amount of gas stretching their intestines. One, Riya's lab partner, doesn't notice a thing. The other, Sam, has a cramping pain low in his belly and spends the assembly planning the fastest route to the restroom. Who is right about how much their gut "should" hurt?

The answer is both of them. Sam (a fictional student who appears throughout this book) has IBS with mixed bowel habits, and gut pain is one of his main symptoms. It flares before big tests and races. He was diagnosed at 15, after tests ruled out other causes, and his gut shows no damage. Yet the pain is as real as a stubbed toe. Meanwhile his best friend Riya, who has Crohn's disease, notices that her pain changes depending on whether her disease is active. During a flare, when her intestine is inflamed, even a normal meal can hurt. In remission, the same meal is usually fine.

Sam and Riya are living examples of this chapter's big idea: **pain is not a simple measure of what is happening in the gut.** It is something the nervous system builds, and the "volume" can be set differently in different people, or in the same person on different days.

8.2 A Smoke Alarm With a Volume Knob

Before we name any nerves, think about a smoke alarm. It has a **detector** that senses smoke, a **circuit board** that decides whether the signal is strong enough to sound the alarm, and a **speaker** that makes the noise.

Now imagine three ways the alarm could start going off at the smell of toast:

1. The detector becomes extra sensitive, so a little smoke looks like a lot.
2. The circuit board turns up its amplifier, so even a weak signal triggers the full alarm.
3. Someone removes the "hush" button that normally lets a person quiet false alarms.

In all three cases, the toast is the same. What changed is the alarm system. The pain system works in a similar way. Sensors in the gut are the detectors. Neurons in the spinal cord are the circuit board. The brain is both the speaker and the person with the hush button. This chapter walks through each part, and the MicroSim later lets you turn each dial yourself.

Pain perception is the brain's construction of the conscious experience of pain from incoming nerve signals, shaped by attention, emotion, memory, and context. Scientists use a separate word, nociception, for the nerve activity caused by a harmful or possibly harmful stimulus. The International Association for the Study of Pain (IASP), the main scientific organization for pain research, revised its official definition of pain in 2020. In short, it describes pain as an unpleasant sensory and emotional experience linked to actual or possible tissue damage, or one that resembles such an experience. Its notes add two points that matter for this chapter: pain and nociception are different things, and pain cannot be inferred just from activity in sensory neurons.

So nerve signals are the raw material, but pain is what the brain makes of them. That is why two people with the same gut stretch can have different pain, and why pain can be real even when no damage shows up on a scan.

Pain is a report, not a ruler



I carry a lot of gut signals up to the brain, and I can tell you the brain doesn't just read them like a ruler. It weighs them against everything else going on, then decides how loud the alarm should be. That makes pain real and adjustable at the same time.

8.3 The Detectors: Nociceptors

Let's start at the detector end. A **nociceptor** is a sensory nerve ending that responds to stimuli that could damage tissue, such as strong pressure, extreme heat, harsh chemicals, or the chemicals released during inflammation. IASP describes nociceptors as high-threshold receptors, meaning they normally need a strong stimulus before they fire. ("Noci" comes from a Latin word for harm.) Nociceptors are not the same as pain. They are detectors that send warning signals; pain happens only if the brain builds an experience from those signals.

Nociceptors are found almost everywhere in the body, but they behave differently in different tissues. That gives us two broad kinds of pain.

Somatic pain is pain that comes from the skin, muscles, bones, and joints (the "body wall"). It is usually sharp or aching and easy to point to. If you cut your finger, you know exactly which finger.

Visceral pain is pain that comes from internal organs (the viscera), such as the stomach, intestines, bladder, or heart. It tends to feel dull, crampy, or deep, and it is hard to pinpoint. A 2016 review of visceral pain by Gebhart and Bielefeldt explains why: internal organs have relatively sparse sensory nerve supply compared with other tissues, and they are supplied by two sets of sensory nerves that overlap in what they do. As a

result, visceral sensations are diffuse and are often felt in other places on the body. The same review notes that about one-third of people with chronic pain report that internal organs contribute to their pain.

The gut's sensory endings respond especially to stretch of the gut wall and to inflammation. The table below sums up the two kinds of pain.

Feature	Somatic pain	Visceral pain
Where it comes from	Skin, muscles, bones, joints	Internal organs, such as the gut
How it feels	Often sharp, clear	Often dull, crampy, deep, or vague
Easy to locate?	Usually yes	Usually no; often felt somewhere else
Density of sensory nerves	Dense	Sparse
Example	Stubbing a toe	Gas or a cramp in the intestine

How do gut signals reach the central nervous system? In Chapter 2 you met the vagus nerve and the spinal afferent nerves. A 2013 review by Brookes and colleagues describes three routes from the gut: a vagal route, and two spinal routes (one entering the spinal cord in the middle and lower back, called thoracolumbar, and one lower down, called lumbosacral). Together these carry feelings of fullness, bloating, nausea, discomfort, urgency, and pain. The roles overlap, but researchers generally describe the spinal afferents as the main pain route from the colon, while the vagus carries mostly non-painful information, such as fullness and nausea. (See Chapter 2 for the vagus side.)

Brookes and colleagues also describe "silent" gut sensory endings, which matter later in this chapter. These endings are quiet most of the time and don't respond to ordinary stretch, but inflammatory chemicals can switch them on. Keep that in mind when we get to Riya's flares.

If you're going through this

If your belly pain is hard to describe, that's not because you're bad at explaining it. Visceral pain really is vague, since the gut has fewer, more spread-out sensors than your skin. Simple notes for your care team can help: when the pain happens, what it feels like, and what was going on that day. Doctors can use patterns like these even when the pain is hard to put into words.

8.4 Why Gut Pain Shows Up in the Wrong Place: Referred Pain

Here is a puzzle. When the heart is starved of oxygen during a heart attack, many people feel pain not in the chest alone but in the left shoulder and arm. The open textbook *Anatomy and Physiology 2e* (OpenStax) uses

exactly this example. Why would the brain put heart pain in the arm?

Referred pain is pain from an internal organ that is felt at a different spot on the body surface, usually skin or muscle supplied by nerves entering the same part of the spinal cord. The leading explanation, according to OpenStax, is that sensory fibers from the organ enter the spinal cord at the same level as sensory fibers from that patch of body surface. OpenStax says the brain then misreads the signal as coming from that body surface. One common way to picture it: signals from the body surface are far more frequent, so the brain bets that the trouble is there. OpenStax also notes that the pattern is not random, but the exact mechanism has not been firmly established.

Think of an apartment building where two apartments share one doorbell wire. When the bell rings, the person at the front desk usually assumes the visitor is for the apartment that gets most of the visitors. They are wrong some of the time, and that is referred pain.

Gut pain follows the same rule. In a classic balloon study of the colon in 1973 (more on it soon), people felt the pain from a balloon in the lower colon in different places: about 40% in the lower middle belly, 31% in one or both sides of the lower belly, 21% in the rectum, and the rest in the back or elsewhere. Same balloon, same spot in the colon, very different locations on the body map. That is why doctors ask detailed questions about pain location, but never rely on location alone.

Pointing is not proof



When your belly hurts "right here," that tells the doctor something useful, but it doesn't pin down which organ is involved. That's normal for visceral pain, so expect questions about timing, triggers, and bowel habits too.

8.5 The Route Up: From the Gut to the Brain

Now we follow the signal upward. You may remember the basic parts of the nervous system from biology class. Neurons pass signals to each other across junctions called synapses, and the spinal cord carries information between the body and the brain. For a deeper refresher on pain pathways, see From Neuron to Bedside, Chapter 6. Here is the short version, focused on the gut.

Step 1: The sensory neuron's home base. A **dorsal root ganglion** is a cluster of sensory neuron cell bodies sitting just outside the spinal cord, on the nerve root that enters the back (dorsal) side of the cord. Each sensory neuron has one long branch reaching out to the gut wall and another reaching into the spinal cord. OpenStax notes that visceral sensory neurons have their cell bodies either in a dorsal root ganglion or in a sensory ganglion of a cranial nerve (for the vagus, that's the nodose ganglion from Chapter 2).

Step 2: The first relay station. The **dorsal horn** is the back part of the spinal cord's gray matter, where incoming sensory neurons form synapses with spinal neurons that carry the signal on toward the brain. This is the "circuit board" in our smoke alarm. As you'll see, signals can be boosted or dampened here.

Step 3: The brain's sorting center. The **thalamus** is a pair of egg-shaped structures deep in the middle of the brain that relays most incoming sensory information to the outer brain (the cortex). OpenStax describes it as a required transfer point for most sensory pathways on their way to the cortex. Pain signals pass through it too.

Step 4: Where the experience is built. From the thalamus, signals reach several cortex areas. Two matter most for gut pain:

- The **insula** is a region of cortex folded deep inside each side of the brain that maps signals from inside the body, such as gut stretch, heartbeat, and breathing. It is a key area for interoception, the sense of the body's internal state that you met in Chapter 2.
- The **anterior cingulate cortex** (ACC) is a strip of cortex near the front of the brain, along the midline just above the band of fibers that connects the two halves of the brain, that helps give pain its unpleasant, emotional, "I need to do something about this" quality and helps focus attention on it.

How do we know these areas are involved? Researchers have used brain scanners (functional MRI and similar tools) while gently stretching the rectum with a balloon. In 2011, Tillisch, Mayer, and Labus pooled the published scanning studies in a meta-analysis (a study that statistically combines the results of many earlier studies). In both people with IBS and healthy volunteers, the stretch consistently activated the thalamus, the insula, and part of the cingulate cortex called the anterior midcingulate. People with IBS showed more consistent activation in regions linked to emotional arousal, including the pregenual part of the anterior cingulate cortex and the amygdala, and in a midbrain area involved in the body's own pain control. Healthy volunteers more often activated parts of the prefrontal cortex linked to thinking and control.

This was a human study, but it shows patterns of brain activity, not cause. It can't tell us whether the brain differences cause IBS symptoms, come from years of having symptoms, or both.

Four stops, that's it



Lots of new names here, so shrink it to four stops: gut sensor, root ganglion, dorsal horn, then thalamus to the insula and ACC. Every "volume knob" in the rest of this chapter sits at one of those stops.

8.6 The Gate in the Spinal Cord

Have you ever bumped your elbow and rubbed it without thinking? Rubbing seems to make it hurt less. In 1965, Ronald Melzack and Patrick Wall published a famous paper in the journal *Science*, called "Pain mechanisms: a new theory," that offered an explanation.

Gate control theory is the idea, proposed by Melzack and Wall in 1965, that the dorsal horn of the spinal cord works like a gate that can let pain signals through to the brain or partly block them, depending on other incoming signals and on signals coming down from the brain. As a 2022 review by Clifford Woolf summarizes it, signals from large touch fibers activate small inhibitory neurons in the dorsal horn, which partly close the

gate on signals from thin pain fibers. Activity in the thin pain fibers does the opposite and opens the gate. The theory also proposed that the brain itself could send signals down to adjust the gate.

So rubbing the elbow sends a flood of touch signals that partly close the gate on the pain signals from the same spot. That's the elbow trick.

Gate control theory changed how scientists think about pain: it is not a straight wire from injury to brain. But Woolf's 2022 review argues that the original wiring diagram is now outdated and oversimplified, since real spinal circuits are far more complex. A fair summary: the circuit Melzack and Wall drew was too simple, but their big idea, that pain signals are adjusted on the way up, has held up.

8.7 The Brain's Volume Knob: Descending Pain Modulation

The gate is not controlled only from below. The brain can reach down and adjust it. **Descending pain modulation** is the brain's ability to turn incoming pain signals down (or up) by sending signals from the brainstem down to the dorsal horn of the spinal cord. A key area for this is the periaqueductal gray, a ring of gray matter around a fluid channel in the midbrain, which works with other brainstem areas.

In the smoke alarm comparison, this is the person with the hush button. Stress can push this system in either direction. A sudden burst of intense stress or fear can turn pain down for a while, which helps explain why an athlete may not notice an injury until after the game; researchers call this stress-induced analgesia. Ongoing stress, worry, and close attention to pain tend to work the other way. In animal studies, many kinds of stress make the gut more sensitive to stretch, and in people, stress is linked to IBS symptoms starting or getting worse. Calm, distraction, and a sense of control can push the system toward turning pain down.

One way researchers test descending control is with a trick: give someone a strong, painful stimulus in one part of the body and see whether pain somewhere else gets weaker. In a healthy nervous system, it often does, as if the brain dampens pain signals across the body when a strong new pain arrives. Researchers call this the "pain inhibits pain" effect, or diffuse noxious inhibitory controls (in human studies it is now usually called conditioned pain modulation). The study below used this test, and a Hype Meter grade follows it (see the Hype Meter if you need a reminder of what the grades mean).

In 2004, Wilder-Smith and colleagues in Switzerland scanned the brains of 10 women with IBS (5 with constipation and 5 with diarrhea) and 10 healthy women. A balloon gently stretched the rectum to cause pain, and the women rated the pain from 0 (none) to 10 (worst). Then the researchers repeated the stretch while each woman put her foot in painfully cold ice water. In healthy women, the ice water lowered rectal pain scores (by a median of 1.5 points on the 10-point scale). In the women with IBS, the ice water did not significantly lower rectal pain. Brain activity in areas including the periaqueductal gray, cingulate cortex, insula, and amygdala also differed between the groups.

How to read a gut-brain claim: the 2004 ice-water study

Question	This study
Mouse or human?	Human. Adult women only.
Correlation or cause?	It compares groups, so it shows a difference linked to IBS, not what caused it. The ice water was an experiment within each person, but nobody was assigned to have IBS. Weaker pain control could contribute to IBS pain, or years of pain could change pain control, or both.
How many?	Very few: 10 women with IBS and 10 healthy women. Results this small can change when repeated.
How long?	One scanning session per person. It can't show whether the difference lasts or changes with treatment.
Who paid for it?	The paper says the study was partly supported by a research grant from AstraZeneca, a drug company.
Is something being sold?	No product is tested or sold in the paper.

The careful conclusion: this small study supports the idea that the brain's built-in pain brakes may work differently in some people with IBS. It does not prove that weak pain brakes cause IBS, and it doesn't tell us about men, teens, or people with other gut conditions. That's why the idea gets a Preliminary grade below.

Hype Meter: "In IBS, the brain's pain brakes don't work"

Strong	Moderate	**Preliminary**	Hype

Verdict: Preliminary. In a 2004 human study of 20 women, a painful ice-water stimulus to the foot reduced rectal pain in healthy women but not in women with IBS, and a meta-analysis of brain scanning studies found differences in a region involved in pain control. These are small or correlational studies, and "don't work" overstates them: the brakes may work differently in some people, not fail in everyone.
What would change the grade: Larger studies with men and women, repeated in different labs, that show weaker descending control predicts who develops IBS pain (not just who already has it), would move it toward Moderate.

8.8 When the Alarm Is Set Too Sensitive: Visceral Hypersensitivity

Now we can name the main idea that connects all of this to IBS. **Visceral hypersensitivity** is a lowered threshold for feeling sensations from internal organs, so that normal amounts of gut stretch or activity are felt as uncomfortable or painful. In smoke alarm terms, the alarm goes off at toast.

How do scientists measure something as personal as gut sensitivity? With a balloon. The **balloon distension test** is a research and specialty test in which a thin, soft balloon is placed in the rectum or colon and slowly or quickly inflated with set volumes or pressures while the person reports when they first feel it, when it feels uncomfortable, and when it hurts. Some versions use a device called a barostat that controls the pressure precisely.

The key study is more than 50 years old. In 1973, the physician J. Ritchie published a study in the journal *Gut*. He inflated a balloon in the lower (pelvic) colon of 67 patients with what was then called "irritable colon syndrome" (today's IBS) and 16 comparison volunteers. When the balloon was inflated to 60 milliliters, 55% of the patients felt pain, compared with only 6% of the comparison group. Ritchie also estimated the tension in the gut wall at that volume and found it was normal in the patients. Their gut wall wasn't being stretched harder. Their nervous systems were reporting the same stretch as pain.

Later studies built on this. In 1995, Mertz and colleagues at UCLA tested 100 people with IBS and 15 healthy controls and reported that 94% of the IBS group showed some form of altered rectal sensation: feeling discomfort at lower volumes, feeling sensations more strongly, or feeling them in unusual places. The hypersensitivity showed up only with fast inflation, not slow. That 94% came from one center and counted any kind of altered sensation, so later reviews describe hypersensitivity as common but not universal. A 2013 review by Farmer and Aziz calls it a key, but not universal, feature. The best summary: **many, but not all, people with IBS have visceral hypersensitivity.**

Does sensitivity actually matter for symptoms? In 2018, Simrén and colleagues combined data from five groups of patients in different countries, 1,144 people with IBS or functional dyspepsia (a disorder of upper-gut pain and fullness), all of whom had had balloon testing. In every one of the five groups, people with higher sensitivity reported more severe gut symptoms. This link remained after the researchers accounted for anxiety, depression, and a general tendency to report body symptoms. The effects were small to medium in size, and the study shows an association, not proof of cause, but it's consistent across countries and methods.

Most people with IBS never have a balloon test. Doctors diagnose IBS from symptoms and a few targeted tests, as you'll see in Chapter 10. Balloon tests are mainly tools for understanding the condition, not for diagnosing a single patient.

Hype Meter: "People with IBS feel gut stretch as painful at lower levels, on average"

Strong	Moderate	Preliminary	Hype

Verdict: Strong. Human balloon studies since 1973 have repeatedly found that, as a group, people with IBS report pain at lower stretch than people without it (55% vs 6% at one volume in the first study), and a 2018 analysis of 1,144 patients in five cohorts linked higher sensitivity to worse symptoms. The words "on average" matter: many people with IBS have normal sensitivity on testing. **What would change the grade:** Little would lower the group finding. Studies showing exactly why some people become hypersensitive, and whether treating it improves symptoms for that subgroup, would add the missing "why."

8.9 Turning Up the Detector: Peripheral Sensitization

Visceral hypersensitivity can come from changes at different stops along the pathway. Let's start at the gut end.

Peripheral sensitization is an increase in how strongly sensory nerve endings in a tissue respond, along with a drop in the stimulus needed to make them fire, usually caused by inflammation or injury in that tissue. IASP defines it as increased responsiveness and a reduced threshold of nociceptive neurons in the periphery. In smoke alarm terms, the detector itself is now extra twitchy.

Inflammation is the classic trigger. When tissue is inflamed, immune cells release chemicals (you met cytokines in Chapter 4) that act directly on nerve endings and make them easier to fire. Remember the "silent" endings from Section 8.3 that wake up in response to inflammatory chemicals? They add to the signal too.

This is what happens to Riya during a Crohn's flare. Her inflamed intestine sends stronger signals from the same meal, so ordinary digestion hurts. When treatment calms the inflammation and she returns to remission, the detectors usually settle back down. The pain followed the inflammation.

What about IBS, where there's no visible inflammation? Some research points to small-scale immune activity. In 2004, Barbara and colleagues in Italy studied colon biopsies (tiny tissue samples) from 44 people with IBS and compared them with healthy controls. Thirty-four of the 44 (77%) had more of the lining taken up by mast cells, the immune cells you met in Chapter 7 that release chemicals such as histamine. Only the mast cells close to nerve fibers (within 5 micrometers, far less than the width of a hair) were linked to how often and how badly people felt pain. This is human evidence, but it's a correlation in one group of patients, not proof that mast cells cause IBS pain.

One more finding matters for people with IBD. A 2020 meta-analysis by Fairbrass and colleagues pooled studies of 3,169 adults with IBD whose disease was in remission. About 32.5% reported symptoms that matched IBS criteria. When remission was confirmed by looking inside the bowel with a scope, the figure was lower but still about 23.5%. People with these IBS-type symptoms also had higher anxiety and depression scores. In other words, some people with IBD keep having gut pain even after the inflammation has calmed,

which suggests the pain system itself may have stayed turned up. This is an association in adults, so it can't tell us the cause, and it doesn't apply automatically to teens.

8.10 Turning Up the Amplifier: Central Sensitization

Now move from the detector to the circuit board. **Central sensitization** is an increase in the excitability of pain-processing neurons in the spinal cord and brain, so that normal or weak incoming signals produce stronger pain responses. In smoke alarm terms, the detector works normally, but the circuit board has cranked up its amplifier.

In 2011, the pain researcher Clifford Woolf described central sensitization in a review as a prolonged but **reversible** increase in the excitability and strength of connections in central pain pathways. It can be triggered in healthy volunteers by strong painful stimuli to the skin, muscles, or internal organs, and it can be seen in changes in brain activity. Woolf lists visceral pain hypersensitivity disorders among the conditions in which central sensitization appears to contribute, along with fibromyalgia, headaches, and some joint and nerve pain.

Two words in that description deserve attention.

- **Reversible** means the amplifier can be turned back down. Central sensitization is a change in how neurons are behaving, not permanent damage.
- **Appears to contribute** means scientists think it plays a role, but it is not the only cause, and there is still no simple test that measures it in one person.

The two kinds connect. Strong or long-lasting signals from an inflamed gut can themselves trigger central sensitization, which may help explain why some people keep having pain after a gut infection or during IBD remission. This idea is still being studied.

Central does not mean imaginary

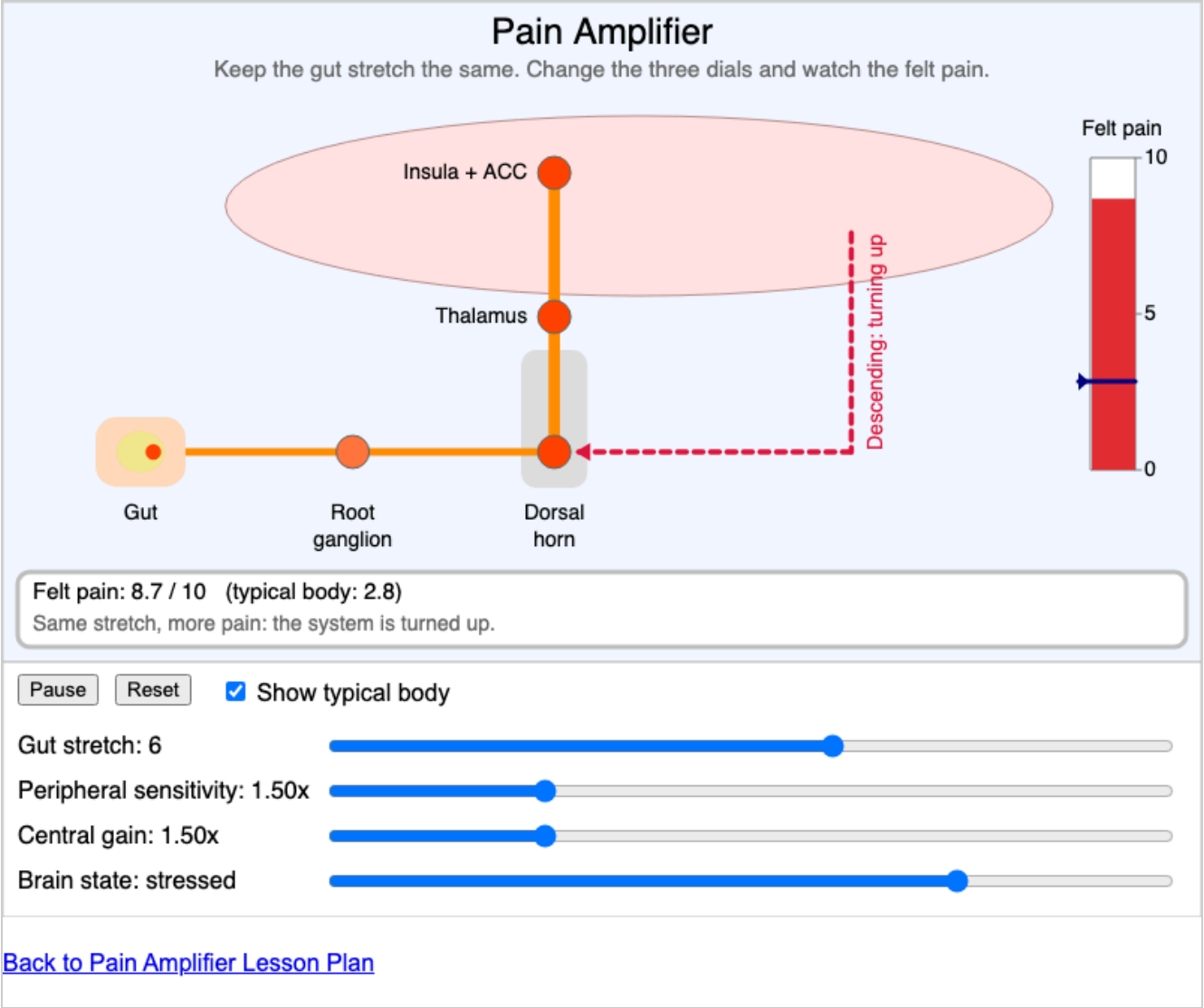


"Central sensitization" means real neurons in the spinal cord and brain are firing more strongly, which you could measure in a lab. It never means "made up." When the amplifier is turned up, the pain is exactly as real as pain from an injury.

8.11 Try It: The Pain Amplifier

You now know three "dials" that can change pain from the same gut stretch. In the simulation below, "peripheral sensitivity" is the detector (peripheral sensitization), "central gain" is the dorsal horn amplifier (central sensitization), and "brain state" is the hush button (descending pain modulation, turning pain down when calm and up when stressed). The meter shows felt pain from 0 to 10, and a navy marker shows what a "typical body" would feel from the same stretch.

Diagram: Pain Amplifier



Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch08-pain-amplifier/main.html

Open the Pain Amplifier fullscreen

MicroSim specification: Pain Amplifier

Type: microsim **sim-id:** ch08-pain-amplifier
Library: p5.js
Status: Implemented
Bloom Level: Understand, Analyze
Bloom Verb: explain, analyze
Learning Objective: The learner will explain how peripheral sensitization, central sensitization, and descending modulation change the pain felt from the same gut stretch, and analyze why a pain score alone cannot show where the signal was amplified.

Canvas: 440 px drawing area plus 170 px controls (iframe 612 px); responsive to about 380 px wide.

Controls: Start/Pause, Reset, Show typical body checkbox; Gut stretch slider (0 to 10, step 1, default 6); Peripheral sensitivity slider (1x to 3x, step 0.25, default 1x); Central gain slider (1x to 3x, step 0.25, default 1x); Brain state slider (very calm, calm, neutral, stressed, very stressed; default neutral).

Rules: Spinal output = stretch x peripheral sensitivity x central gain x descending factor (0.6, 0.8, 1.0, 1.2, 1.4 from very calm to very stressed). Below a threshold of 4 (arbitrary units) nothing is felt. Above it, felt pain = 10 x (1 - e^(-(output - 4)/6)), so pain rises and levels off near 10. The typical body uses all dials at their defaults.

Feedback: Signal dots and path thickness grow with signal strength; the descending line turns green (calm) or red (stressed); a readout compares felt pain with the typical body and names the state.

Provenance: Sections 8.6 to 8.10 (Woolf 2011; Wilder-Smith 2004; Gebhart and Bielefeldt 2016; IASP terminology). All numbers are illustrative teaching values.

Start with every dial at its default and press Start. With a gut stretch of 6, the typical body feels mild pain. Now drop the stretch to 3: the signal still travels up the spinal cord, but it stays below the threshold, so it is sensed but not felt as pain. That's like most of the gut activity you never notice. Set the stretch back to 6 and raise peripheral sensitivity to 2x. The same stretch now hurts much more, which is roughly what happens to Riya during a flare.

Next, reset and raise only the central gain. Notice that a boost in the spinal cord gives the same felt pain as the same boost in the gut. The meter can't tell where the amplification happened, and neither can a pain score in a clinic. Finally, with central gain at 2x, slide the brain state from "very calm" to "very stressed," the kind of swing Sam feels before a race. The gut hasn't changed at all, yet the pain moves several points.

What this model leaves out

- Real pain is built from many signals at once (stretch, chemicals, inflammation, motility), not one stretch slider.
- Peripheral and central sensitization interact over time; strong gut signals can cause central sensitization, which the sim treats as separate, fixed dials.
- The brain's influence includes attention, memory, expectations, mood, and sleep, not just a single calm-to-stressed slider. In the sim, "stressed" always turns pain up, but a sudden, intense stress can sometimes turn pain down for a while (stress-induced analgesia).
- The vagus nerve, the many brain regions involved, and the emotional side of pain are left out or shown as single dots.
- The threshold, the multipliers, and the 0 to 10 output are made-up teaching numbers. The sim cannot predict any real person's pain.

8.12 Thoughts, Feelings, and the Volume of Pain

The brain doesn't adjust pain only through automatic circuits. What we expect, fear, and pay attention to also feeds into the descending system. This is where many people with chronic pain start to feel blamed, so let's be careful and precise.

Pain catastrophizing is a pattern of thinking about pain in which a person tends to dwell on it, expect the worst from it, and feel helpless to do anything about it. The term comes from pain psychology. The most widely used questionnaire, the Pain Catastrophizing Scale (developed by Sullivan and colleagues in 1995), measures three parts: rumination (not being able to stop thinking about the pain), magnification (seeing the pain as more threatening), and helplessness (feeling nothing can be done).

The name sounds harsh, but it doesn't mean "overreacting." It describes a common, understandable pattern that often grows when pain is unpredictable, unexplained, or not believed. Researchers study it because it seems to turn the pain volume up, possibly through descending pathways, and because it can change with practice.

For example, in a 2018 study of 261 children with IBS (average age about 10), Hollier and colleagues found that pain catastrophizing partly accounted for the link between anxiety and how severe the children's abdominal pain was. Children with more anxiety tended to catastrophize more, and more catastrophizing went with worse pain. The authors pointed out that their design (measuring everything at one time point) can't prove cause. It's a human, correlational finding, but it suggests that thinking patterns about pain may be a useful target for treatment.

This connects to treatment. Brain-gut behavioral therapies, such as cognitive behavioral therapy (CBT) and gut-directed hypnotherapy, teach skills to change how the brain responds to gut signals. In a 2024 network meta-analysis of 42 randomized trials with 5,220 people with IBS, Goodoory and colleagues found that several

of these therapies, including self-guided CBT and face-to-face gut-directed hypnotherapy, may improve abdominal pain more than control treatments. No trial was at low risk of bias in every area, so the size of the benefit may be overestimated.

The 2021 American College of Gastroenterology IBS guideline also suggests gut-directed psychotherapy for overall IBS symptoms ("suggests" is the guideline's word for a conditional recommendation, weaker than "recommends"). Some doctors also use certain medicines at low doses as "gut-brain neuromodulators," which act on nerve signaling to dial pain down; using them doesn't mean a person's pain is caused by depression or anxiety. You'll learn more about these treatments in Chapter 10 and Chapter 18.

None of this says "the pain is psychological." Researchers think these therapies work partly through the same pain-control circuits that the brain scans point to. Changing the brain's response to a real signal is a real treatment for a real problem.

Living with pain that comes back again and again can also wear down a person's mood. Long-lasting pain, poor sleep, and worry tend to feed each other, and people with chronic gut pain have higher rates of anxiety and depression symptoms, as Chapter 11 explains. If pain is making you feel hopeless, that deserves care just as much as the pain itself.

If you are struggling right now

If you are thinking about suicide or are in crisis, call or text **988** to reach the 988 Suicide & Crisis Lifeline (in the US), or go to the nearest emergency room. Outside the US, you can find a helpline at findahelpline.com. You can also talk to a parent, school counselor, or doctor.

For families

When a teen's tests come back normal, it can be tempting to feel relieved and say, "See, there's nothing wrong." To a teen in pain, that can sound like "we don't believe you." Try "I'm glad it's nothing dangerous. Let's figure out how to make it hurt less." Avoid asking "Is it really that bad?" and instead ask what helps and what makes it worse. Helping a teen keep up with school, sleep, and friends, while working with the care team on a plan, usually helps more than either pushing through or stopping everything.

8.13 "It's All in Your Head": Why That Phrase Is Wrong

Let's put the chapter together and grade the claim that hurts many people with gut pain the most.

Normal blood work, stool tests, or a colonoscopy show that certain diseases (like inflammation, bleeding, infection, or cancer) are unlikely. They don't measure how sensitive the nerves are, how much the dorsal horn amplifies signals, or how well the brain's pain brakes work. Those are real biological processes, but they don't show up on a standard scan.

A 2019 review by Grundy, Erickson, and Brierley estimates that chronic visceral pain affects more than 20% of people worldwide (including pelvic and bladder pain, not only the gut), often with no obvious structural cause. If "normal tests" meant "imaginary," a huge share of humanity would be imagining their pain.

Hype Meter: "If your tests are normal, the pain is in your head"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. Standard tests look for structural disease, not for how sensitive the pain system is. Human balloon studies since 1973 show that many people with IBS feel normal gut stretch as painful while their gut wall tension is normal, and brain scans show real differences in how the brain processes gut signals. Pain always involves the brain, but that makes it real, not imaginary. **What would change the grade:** Nothing realistic. The careful version, "normal tests can mean the pain comes from a sensitized pain system rather than damage," is already well supported.

At the Bedside: A Year of Belly Pain and Normal Tests

Meet the patient (fictional)

Nadia is 17 and a high school senior. For about a year she has had cramping lower-belly pain several days a week, often after meals and a little better after a bowel movement. Her stools switch between loose and hard. She has quit her dance class and skips lunch because she worries the pain will hit in class. An emergency room visit ended with "Everything looks fine," and her mom has started to wonder if Nadia is exaggerating. So has Nadia.

What the doctor checks: A pediatric gastroenterologist takes a detailed history: when the pain happens, how it relates to bowel movements, what her stools are like, and whether there are warning signs such as blood in the stool, weight loss, waking at night with diarrhea, fever, or a family history of IBD or celiac disease. Nadia has none. The doctor examines her belly and orders a few targeted tests: blood tests, a celiac blood test, and a stool test for inflammation (fecal calprotectin, which you'll meet in Chapter 9). All are normal. No balloon test is needed, because IBS can be diagnosed from symptoms plus limited testing.

Connecting the signals: Normal tests make inflammation, celiac disease, and other structural problems unlikely. But her months of pain linked to bowel movements and stool changes fit a disorder of gut-brain interaction. The doctor uses a picture like this chapter's smoke alarm: her nervous system is likely turning normal gut activity up into pain (visceral hypersensitivity), and her fear of pain in class may be raising the volume further through descending pathways.

Diagnosis: Irritable bowel syndrome (IBS) with mixed bowel habits, a disorder of gut-brain interaction. (Chapter 10 covers how IBS is diagnosed.)

Why it happens: Visceral hypersensitivity can come from peripheral sensitization in the gut, central sensitization in the spinal cord and brain, and differences in descending pain modulation. Researchers don't yet know which mix applies to Nadia. Her pain is real because the signals and the amplification are real.

The mind-body side: The doctor says clearly, "Your pain is real, even though your tests are normal," and Nadia cries with relief. The team suggests her mom believe Nadia's reports while helping her slowly return to routines like dance. Nadia is referred to a psychologist who works with gut conditions, and her school counselor sets up a restroom pass so she doesn't have to explain herself.

Treatment today: Her plan may include learning how the gut-brain pain system works, a brain-gut behavioral therapy such as CBT or gut-directed hypnotherapy, a visit with a dietitian, and possibly a medicine her doctor chooses, such as a low-dose gut-brain neuromodulator. Her doctor explains that these medicines act on pain signaling and don't mean her pain is "really depression." Medicine decisions belong to Nadia, her family, and her doctor.

What's new in research: In 2026, Algera and colleagues in Sweden reported a non-invasive test of gut sensitivity in which people drink a sugar solution (lactulose with a nutrient drink) and rate symptoms such as pain and bloating for 4 hours. The researchers set the cutoff for "hypersensitive" from how 133 healthy volunteers responded, and by that cutoff, 76% of 273 people with IBS were hypersensitive. Those with lower rectal pain thresholds on balloon testing were more likely to be hypersensitive, but so were people whose gut bacteria made more hydrogen gas from the sugar, so the test measures gas production as well as nerve sensitivity. **Evidence grade: Preliminary.** It is one study from a single research group that defined its own cutoff, and other centers need to repeat it before it could become a routine test.

Your turn: reason through a variation

Riya has been in remission from Crohn's disease for eight months. Her latest stool calprotectin and her colonoscopy showed no active inflammation, but she has started having crampy belly pain again before orchestra concerts. Using this chapter, how would you reason about this?

Answer: The first step belongs to her care team: make sure there is no new inflammation, since a flare must be found and treated. If her disease really is quiet, her pain could still be real. Studies of adults with IBD in remission find that about a quarter to a third report IBS-type symptoms, possibly because earlier inflammation left the pain system more sensitive (peripheral and central sensitization), and pre-concert stress could be turning the volume up through descending pathways. Her team might then add gut-brain approaches rather than stronger IBD medicines.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: The amount of pain always matches the amount of damage in the body.
Reality: Pain is built by the nervous system from signals that can be turned up or down at several stops. A gut with no visible damage can hurt a lot, and some damage causes little pain.

Myth: Gut pain is easy to locate, so where it hurts tells you which organ is the problem.
Reality: Visceral pain is vague because internal organs have sparse, overlapping sensory nerves, and it is often referred to other spots on the body. In Ritchie's 1973 balloon study, the same balloon in the colon was felt in the lower belly, the sides, the rectum, or the back.

Myth: More pain always means the disease is getting worse.
Reality: Pain can rise because the pain system is more sensitive, because of stress, or because of poor sleep, without any change in disease. For people with IBD, new pain still needs to be checked by the care team, but some people in remission have IBS-type pain without active inflammation.

Myth: Central sensitization means the pain is imaginary or "all in your head."
Reality: Central sensitization is a measurable increase in the excitability of real neurons in the spinal cord and brain. It is reversible, and the pain it causes is as real as pain from an injury.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Doctors couldn't find anything wrong, so my IBS pain is just stress. If I relax enough it will go away for good."

Grade: Hype. The claim mixes something true with two leaps. It's true that stress can turn pain up through descending pathways, and in randomized trials, therapies that calm the brain's response to gut signals may reduce pain (moderate-quality evidence). But IBS pain also involves visceral hypersensitivity, which can come from peripheral and central sensitization, not stress alone, and "go away for good" promises more than any study shows. A careful version: "Normal tests don't mean my pain isn't real. Stress can make it worse, and brain-gut therapies can help many people feel less pain."

2. Predict: Sam takes a balloon distension test on a calm, rested morning, and again the morning of the state cross-country meet. Predict how his pain ratings might differ, and explain the pathway.

His pain ratings would likely be higher on race morning, at the same balloon volume. Stress and worry can push descending pain modulation toward turning signals up at the dorsal horn, and attention to his gut may raise the volume further. His gut stretch is the same both days; what changes is how much the signal is amplified on its way to the brain. (This is a prediction from the model in this chapter, not a result from a specific study of race days. A sudden, intense stress can sometimes dampen pain instead, so the real answer could vary.)

3. Explain: Why might Riya's belly hurt after an ordinary meal during a flare, but not in remission?

During a flare, her inflamed intestine releases inflammatory chemicals that act on nerve endings. This peripheral sensitization lowers the threshold for those endings to fire and can wake up normally silent endings, so the same meal produces a stronger signal. When treatment calms the inflammation, the endings usually settle back toward normal sensitivity, and ordinary meals stop hurting.

4. Apply: A heart attack can cause pain in the left arm. A student says, "That proves the pain signal travels to the arm." Use referred pain to correct the student.

The signal doesn't travel to the arm. Sensory fibers from the heart enter the spinal cord at the same level as fibers from the shoulder and arm, so they share relay neurons. The brain receives the signal on that shared line and, since arm signals are much more common, interprets it as coming from the arm. The pain is felt in the arm, but its source is the heart.

5. Read the data. In a classic balloon study of the colon (Ritchie, 1973, *Gut*), a balloon was inflated to 60 milliliters in the lower colon of each person. Here is how many felt pain:

Group	Number of people	Felt pain at 60 mL
People with irritable colon syndrome (IBS)	67	55%
Comparison group (healthy and constipated volunteers)	16	6%

5. What does this data show, and what can't it show?

It shows that, as a group, people with IBS were far more likely to feel pain at the same balloon volume: 55% versus 6%. Since Ritchie also found normal gut wall tension in the patients, it supports a more sensitive pain system, not a harder stretch. It can't show cause (did sensitivity lead to IBS, or did IBS lead to sensitivity?), and the comparison group was tiny (16 people, so 6% is about 1 person) and included constipated volunteers. It also can't tell us about any individual, since 45% of the patients felt no pain at that volume. A helpful follow-up: a larger study that measures sensitivity before people develop IBS, such as after a gut infection, and follows them over time.

Exercises

Remember

1. What is the difference between a nociceptor and pain?

Answer

A nociceptor is a sensory nerve ending that responds to stimuli that could damage tissue. Pain is the experience the brain builds from signals like these, shaped by context, attention, and emotion. Nociceptor activity can happen without pain, and pain cannot be inferred just from sensory neuron activity.

1. List the four main stops a gut pain signal passes on its way to being felt.

Answer

Sensory nerve endings in the gut, the dorsal root ganglion (where the sensory neuron's cell body sits), the dorsal horn of the spinal cord, and the thalamus, which relays signals to cortex areas such as the insula and anterior cingulate cortex.

Understand

1. Explain why visceral pain is harder to locate than somatic pain.

Answer

Internal organs have relatively sparse sensory nerves, supplied by two overlapping sets of nerves, so the signals are diffuse. Visceral fibers also share spinal relay neurons with body-surface fibers, so the brain often refers the pain to skin or muscle. The skin, by contrast, has dense sensory nerves and a precise body map.

1. In your own words, explain the difference between peripheral sensitization and central sensitization.

Answer

Peripheral sensitization happens at the detector end: nerve endings in the gut become more responsive, often because of inflammation. Central sensitization happens in the spinal cord and brain: pain-processing neurons become more excitable, so even normal incoming signals cause stronger pain. Both can lead to visceral hypersensitivity, and strong peripheral signals can trigger central sensitization.

Apply

1. Using the Pain Amplifier MicroSim, find two different combinations of dials that give a felt pain of about 6 with a gut stretch of 6. Describe both, then explain why a doctor who knows only a patient's pain score can't tell which "dial" is turned up.

2. A friend with IBS tells you their pain is worse during finals week, even though they're eating the same foods. Use descending pain modulation and the smoke alarm comparison to explain this to them in three or four sentences, without suggesting the pain is imaginary.

Analyze

1. Compare the Ritchie 1973 study and the Simrén 2018 study. For each, answer three of the six questions (mouse or human, correlation or cause, how many). What does the newer study add that the older one couldn't show?
2. The Fairbrass 2020 meta-analysis found that about 32.5% of adults with IBD in remission had IBS-type symptoms, but only about 23.5% when remission was confirmed with a scope. Analyze why the way remission was defined changed the number, and what that suggests about some of the "IBS-type" pain in the larger group.

Evaluate

1. Some patients dislike the term "pain catastrophizing" because it sounds like blame. Evaluate whether researchers should keep using it. Give one argument for keeping it, one for replacing it, and your judgment, using evidence from Section 8.12.
2. Evaluate this headline: "Brain scans prove IBS is a brain disease, not a gut disease." Use the Tillisch 2011 meta-analysis, the Barbara 2004 mast cell study, and at least two of the six questions to decide what grade the headline deserves.

Create

1. Design a study to test whether gut-directed hypnotherapy reduces visceral hypersensitivity in teens with IBS. Describe your groups, how you would measure sensitivity before and after, how long you would follow participants, and the result that would support your hypothesis.
2. Create a one-page handout for a school nurse titled "When a Student Has Gut Pain and Normal Tests." Use at least three ideas from this chapter (such as visceral hypersensitivity, central sensitization, or descending modulation) in plain language, and include two things the nurse should say and one thing to avoid saying.

Key Takeaways

- Pain perception is built by the brain from nerve signals. Pain and nociception are different, and pain can't be read directly from sensory neuron activity.

- Visceral pain from the gut is dull, vague, and often referred to other places on the body, because the gut has sparse, overlapping sensory nerves that share spinal relay neurons with the body surface.
- A gut pain signal travels from nociceptors in the gut wall to the dorsal root ganglion, the dorsal horn, the thalamus, and cortex areas including the insula and anterior cingulate cortex.
- Pain signals are adjusted on the way up: gate control theory proposed that the spinal cord can act like a gate, and descending pain modulation lets the brain turn signals down or up.
- Visceral hypersensitivity is common, but not universal, in IBS. Balloon distension tests since 1973 show that many people with IBS feel normal gut stretch as painful, and higher sensitivity goes with worse symptoms.
- Sensitivity can be turned up at the gut (peripheral sensitization, often from inflammation) or in the spinal cord and brain (central sensitization, which is real and reversible), and thinking patterns such as pain catastrophizing can raise the volume further.
- Normal tests never mean imaginary pain. In randomized trials, brain-gut therapies such as CBT and gut-directed hypnotherapy can reduce IBS pain (moderate-quality evidence), likely by working on real pain circuits.

You traced pain from gut to brain!



You can now explain why the same gut stretch can hurt one person and not another, and why "your tests are normal" is the start of a conversation, not the end. Next, in Chapter 9, we'll follow Riya's story into inflammatory bowel disease, where the gut really is inflamed and the pain system is only part of the picture.

Quiz: Pain, Sensitivity, and the Gut

Test your understanding of Chapter 8. Choose the best answer, then click **Show Answer** to check.

Question 1

What is a nociceptor?

A. A brain area that creates the emotional feeling of pain

B. A sensory nerve ending that responds to stimuli that could damage tissue

C. A spinal cord neuron that blocks all pain signals

D. A chemical released by mast cells during inflammation

Show Answer

The correct answer is **B**. A nociceptor is a high-threshold sensory nerve ending that responds to harmful or possibly harmful stimuli, such as strong pressure or inflammatory chemicals. Option A describes areas like the anterior cingulate cortex; nociceptors only detect, and pain itself is built by the brain.

Concept Tested: Nociceptor **Bloom's Level:** Remember

Question 2

Which structure acts as a relay station that passes most incoming sensory signals, including pain signals, on to the cortex?

A. The dorsal root ganglion

B. The insula

C. The enteric nervous system

D. The thalamus

Show Answer

The correct answer is **D**. The thalamus, deep in the middle of the brain, is a required transfer point for most sensory pathways on their way to the cortex. The dorsal root ganglion (A) holds the cell bodies of sensory neurons outside the spinal cord, so it comes earlier in the pathway.

Concept Tested: Thalamus **Bloom's Level:** Remember

Question 3

What did Melzack and Wall's gate control theory (1965) propose?

A. The dorsal horn of the spinal cord can let pain signals through or partly block them, depending on other signals

B. Pain signals travel in a straight, unchangeable line from the injury to the brain

C. The gut has a gate that closes when food is digested

D. Pain is felt only when the brain releases a pain chemical

Show Answer

The correct answer is **A**. Gate control theory proposed that the dorsal horn works like a gate, with touch signals helping close it and pain-fiber signals opening it, and with input from the brain adjusting it. Option B is the older "straight wire" view the theory challenged. Today the original circuit is considered too simple, but the idea that signals are adjusted on the way up has held.

Concept Tested: Gate Control Theory **Bloom's Level:** Remember

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Question 4

Why is pain from the intestines usually harder to pinpoint than pain from a cut finger?

A. The intestines have no sensory nerves at all

B. Gut pain signals travel only through the vagus nerve, which can't carry location

C. Internal organs have sparse, overlapping sensory nerves, and their signals share spinal relays with the body surface

D. Gut pain is weaker, so the brain ignores where it comes from

Show Answer

The correct answer is **C**. The viscera have relatively sparse sensory nerve supply from two overlapping sets of nerves, so the signals are diffuse, and they share spinal relay neurons with skin and muscle, which leads to referred pain. Option A is wrong: the gut has sensory nerves, which is why stretch and inflammation can hurt.

Concept Tested: Visceral Pain **Bloom's Level:** Understand

Question 5

In Ritchie's 1973 balloon study, 55% of patients with irritable colon syndrome felt pain at 60 mL versus 6% of the comparison group, yet the gut wall tension in the patients was normal. What does the normal wall tension suggest?

A. The patients' guts were being stretched much harder than the comparison group's

B. The patients' nervous systems were reporting the same stretch as more painful

C. The patients were pretending to feel pain

D. The balloon was broken during the patients' tests

Show Answer

The correct answer is **B**. If the gut wall was under normal tension, the stretch itself wasn't stronger. The difference was in how the nervous system handled the signal, which is visceral hypersensitivity. Option C confuses "no extra stretch" with "no real pain"; the pain was real, but the sensitivity was higher.

Concept Tested: Balloon Distension Test **Bloom's Level:** Understand

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Question 6

Which statement best describes central sensitization?

A. A reversible increase in the excitability of pain-processing neurons in the spinal cord and brain

B. Permanent damage to the brain caused by long-lasting pain

C. Pain that a person imagines because they are worried

D. Increased sensitivity of nerve endings in an inflamed gut

Show Answer

The correct answer is **A**. Central sensitization is a measurable, reversible increase in how strongly central pain neurons respond, so weak or normal signals cause stronger pain. Option D describes peripheral sensitization, which happens at the nerve endings in the tissue, not in the spinal cord and brain. Option C is a harmful myth: the pain is real.

Concept Tested: Central Sensitization **Bloom's Level:** Understand

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Question 7

During a Crohn's flare, Riya notices that an ordinary dinner makes her belly hurt, even though the same meal is fine when she's in remission. Which mechanism best explains the difference?

A. Gate control: the touch fibers in her belly have stopped working

B. Referred pain: the pain is coming from her arm

C. Pain catastrophizing: she is exaggerating the pain

D. Peripheral sensitization: inflammation makes the gut's nerve endings fire more easily

Show Answer

The correct answer is **D**. Inflammatory chemicals released during a flare act on nerve endings in the gut, lowering their threshold and waking up normally silent endings, so the same meal produces a stronger signal. Option C wrongly treats a biological change as exaggeration; nothing in her story suggests her thinking changed, but her gut's inflammation did.

Concept Tested: Peripheral Sensitization **Bloom's Level:** Apply

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Question 8

A soccer player twists her ankle badly in the final minutes of a big game but doesn't notice much pain until she sits on the bench afterward. Which idea from this chapter best explains this?

A. Visceral hypersensitivity

B. Peripheral sensitization

C. Descending pain modulation

D. Referred pain

Show Answer

The correct answer is **C**. During intense focus and excitement, signals from the brainstem down to the dorsal horn can turn incoming pain signals down. Once she relaxes, that dampening fades and the pain is felt. Option B would make the ankle hurt more, not less, and it develops as the tissue becomes inflamed.

Concept Tested: Descending Pain Modulation **Bloom's Level:** Apply

---

Question 9

In a 2004 study of 10 women with IBS and 10 healthy women, painful ice water on the foot lowered rectal pain in the healthy women but not significantly in the women with IBS. Which conclusion does this study best support?

A. The brain's built-in pain-dampening system may work differently in some people with IBS

B. Weak pain brakes are proven to cause IBS in everyone

C. Ice water is an effective treatment for IBS pain

D. Men with IBS have stronger pain brakes than women with IBS

Show Answer

The correct answer is **A**. The study suggests a difference in descending pain control in this small group, which is why it earns a Preliminary grade. Option B overreaches: 20 people, one session, and a group comparison can't prove cause or apply to everyone. Option D can't be judged, since no men were studied.

Concept Tested: Descending Pain Modulation **Bloom's Level:** Analyze

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Question 10

A 2020 meta-analysis found that about 32.5% of adults with IBD in remission reported IBS-type symptoms, but only about 23.5% when remission was confirmed by looking inside the bowel with a scope. What is the best explanation for the difference?

A. Scopes cause IBS-type symptoms

B. Some people counted as "in remission" by symptom scores may still have had hidden inflammation causing pain

C. IBS-type symptoms are imaginary in people with IBD

D. The scope studies included only children

Show Answer

The correct answer is **B**. Symptom-based definitions of remission can miss ongoing inflammation, which would add inflammation-driven pain to the "IBS-type" group. Even with strict scope-confirmed remission, about a quarter still had symptoms, which suggests a sensitized pain system in some people. Option D is wrong because the meta-analysis studied adults.

Concept Tested: Visceral Hypersensitivity **Bloom's Level:** Analyze

Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's

Summary

Inflammatory bowel disease (IBD) is a group of long-lasting conditions in which the immune system keeps attacking the gut wall. Its two main forms, ulcerative colitis and Crohn's disease, differ in where they strike and how deep the damage goes. This chapter follows Riya from her first symptoms to remission: how doctors find the inflammation with a stool test and a colonoscopy, how the treatment toolbox works (from steroids to biologic medicines), and why the modern goal is a healed gut lining, not just fewer symptoms. It also explores how gut inflammation reaches the brain, why anxiety and low mood are common during flares, and why stress and diet have not been shown to cause IBD, even though both can matter for how people feel.

Concepts Covered

1. Immune-Mediated Disease
2. Inflammatory Bowel Disease
3. Ulcerative Colitis
4. Crohn's Disease
5. Transmural Inflammation
6. Disease Flare
7. Remission
8. Extraintestinal Manifestation
9. IBD Risk Factors
10. Pediatric IBD
11. Colonoscopy
12. Fecal Calprotectin
13. Aminosalicylate
14. Corticosteroid
15. Immunomodulator
16. Biologic Therapy
17. Anti-TNF Therapy

18. JAK Inhibitor
19. Mucosal Healing
20. IBD Surgery

Prerequisites

- Chapter 3: Meet the Microbiome (gut microbes and dysbiosis)
- Chapter 4: The Immune System as a Sense Organ (inflammation, cytokines, and how they reach the brain)
- Chapter 7: Stress and the Gut (the HPA axis and how stress changes gut function)
- Chapter 8: Pain, Sensitivity, and the Gut (visceral pain and sensitization)

When the gut's defenses won't stand down



This is Riya's chapter. About 100,000 American kids and teens live with IBD, so there's a good chance someone in your school does, even if you'd never know it. Knowing what's actually happening inside their gut, and inside their head during a flare, makes it much easier to be a good friend to them. Let's check what the gut is really telling the brain!

9.1 A Word Riya Had Never Heard

Riya was 13 when the stomachaches started. At first they came and went, and her family blamed spicy food or a stomach bug. By the spring of eighth grade she was running to the bathroom several times a day, often with cramping pain low on the right side of her belly. She stopped finishing the dal and rice her grandmother made, because eating seemed to make the pain worse. Her jeans got loose. She fell asleep over homework, and her violin teacher asked if she was all right. (Riya is a fictional student who appears throughout this book.)

After months of this, her pediatrician ordered a stool test, then sent her to a pediatric gastroenterologist, Dr. Alvarez. A few weeks later Riya was lying in a recovery room after her first colonoscopy, still groggy, when Dr. Alvarez sat down with her parents and said a word Riya had never heard: "Crohn's." Riya was 14. Her first question was, "Did I do something to cause this?" Her second was, "Will it go away?" This chapter answers both questions honestly. The short answers are "no" and "not completely, but it can be controlled."

9.2 A Security System That Won't Stand Down

Before any technical names, picture a building with a very good security system. Normally, when a real intruder shows up, the alarm sounds, guards rush in, the intruder is handled, and the guards go back to their posts. Now imagine the system starts treating the building's own friendly visitors as intruders. The alarm keeps ringing, the guards keep arriving, and in the scuffle they break windows and damage walls. Nobody broke in. The damage comes from the defenders themselves.

That is roughly what happens in inflammatory bowel disease. Your gut lining is a border between your body and trillions of microbes (Chapter 3), and your gut immune system patrols that border constantly (Chapter 4). In IBD, the patrol overreacts and won't calm down.

An **immune-mediated disease** is a condition in which the body's own immune response, rather than an outside germ or a toxin, causes most of the damage. IBD belongs to this family, along with conditions such as rheumatoid arthritis and psoriasis.

Inflammatory bowel disease (IBD) is a group of chronic conditions in which abnormal immune reactions cause long-lasting, recurring inflammation of the digestive tract. "Chronic" means long-lasting, often lifelong. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) describes both main forms of IBD as chronic diseases in which abnormal reactions of the immune system cause inflammation in the gut. A 2021 review in *Lancet Gastroenterology & Hepatology* calls IBD a lifelong condition with no cure.

"No cure" can sound scary. The other half of the story is that there are many treatments that can calm the inflammation, let the gut heal, and keep people well for long stretches.

Inflammation is the real target



I want you to hold one idea through this whole chapter: in IBD, the symptoms come from inflammation you can actually see and measure in the gut wall. That's what makes IBD different from IBS in Chapter 10, where the gut looks normal but the gut-brain conversation is off.

9.3 Two Main Types: Ulcerative Colitis and Crohn's Disease

IBD has two main forms. (A third, called microscopic colitis, mostly affects older adults and isn't covered here. And some people, especially young children, have colitis that doesn't clearly fit either main form at first; doctors call this IBD-unclassified, according to the revised Porto criteria for diagnosing IBD in children.) They share a lot, but they differ in two big ways: **where** the inflammation happens and **how deep** it goes.

Ulcerative colitis (UC) is a form of IBD in which inflammation affects only the large intestine (colon) and rectum, starting at the rectum and spreading upward in one continuous stretch, and stays in the inner layers of the gut wall. Recall the four gut wall layers from Chapter 1: mucosa, submucosa, muscularis, and serosa. In UC, the inflammation stays in the inner layers, the mucosa and submucosa, according to the StatPearls review of ulcerative colitis. Most of it is in the innermost lining, the mucosa, which is how the FDA describes UC. The inflamed lining develops sores called ulcers, which bleed. A 2023 review in *The Lancet* by Le Berre and colleagues says people with UC usually first see a doctor because of bloody diarrhea. Other common symptoms, according to NIDDK, are belly cramps, mucus in the stool, an urgent need to go, and a feeling of needing to go even when the bowel is empty.

Crohn's disease is a form of IBD that can affect any part of the digestive tract, from the mouth to the anus, most often the end of the small intestine (the ileum) and the beginning of the colon, often in patches with

healthy sections in between. Doctors call those healthy gaps "skip lesions." Riya's Crohn's affects the end of her small intestine and part of her colon, the most common pattern. A 2024 *Lancet* review by Dolinger, Torres, and Vermeire describes Crohn's inflammation as often patchy and segmental, commonly in the terminal ileum and nearby colon. NIDDK lists diarrhea, belly cramps and pain, and weight loss as the most common symptoms.

The second big difference is depth. **Transmural inflammation** is inflammation that extends through the entire thickness of the gut wall, from the inner lining all the way to the outer layer. ("Trans" means across, and "mural" means wall.) Crohn's disease is transmural; ulcerative colitis usually is not.

Why does depth matter? Picture a garden hose. If irritation eats through every layer, the hose can scar and narrow, or spring a hole that tunnels into something nearby. Deep inflammation in Crohn's can cause:

- **Strictures:** scarred, narrowed sections of bowel that can block the flow of food and stool.
- **Fistulas:** abnormal tunnels from the bowel to another organ or to the skin.
- **Abscesses:** pockets of pus from infection.

According to the StatPearls review of Crohn's disease, about half of patients develop one of these complications within 20 years of diagnosis. This is one reason doctors now treat Crohn's early and aim to heal the lining before damage builds up (Section 9.9).

The table sums up the differences.

Feature	Ulcerative colitis	Crohn's disease
Where	Colon and rectum only	Anywhere from mouth to anus; most often end of small intestine and start of colon
Pattern	Continuous, starting at the rectum	Patchy, with healthy "skip" areas
Depth	Inner layers (mostly the mucosa)	Transmural (through the whole wall)
Typical first complaint	Bloody diarrhea	Diarrhea, belly pain, weight loss
Possible complications	Severe bleeding, a dangerously swollen colon	Strictures, fistulas, abscesses
Can surgery remove the disease?	Removing the colon and rectum removes the disease from the gut	No; it can come back in another part of the gut

A memory hook for the two types



Ulcerative **colitis** has "colon" right in the name, so it stays in the colon and rectum. **Crohn's** can "roam": any part of the gut, in patches, through every layer.

9.4 How Common Is IBD, and Who Gets It?

IBD isn't rare, though counting it is tricky. One method uses insurance claims, the billing records that show who was actually diagnosed and treated. Another is a survey asking adults whether a doctor ever told them they had the disease. They measure different things, so they give different numbers.

Using claims data, a 2023 study in *Gastroenterology* led by James Lewis estimated that IBD is diagnosed in about 721 of every 100,000 Americans, roughly 0.7% of the population, or about 2.39 million people. A 2025 study by Kappelman and colleagues, using the same kind of data, found about 122 cases per 100,000 people under age 20, or roughly 100,000 young people.

National surveys give a higher number: in 2023 to 2024, 1.6% of US adults (about 4.1 million) said a doctor had told them they had Crohn's disease or ulcerative colitis, according to a 2026 report from the National Center for Health Statistics. Surveys count anyone who was ever told they had the disease, which can include old or mistaken diagnoses, so the claims figure is probably the better estimate of how many people are living with diagnosed IBD. (Claims data have gaps too: they can't count people who had no insurance record in the years studied.)

IBD can start at any age, but it most often begins in young adulthood. The Lewis study found that new diagnoses peak in people's twenties. NIDDK says UC most often begins between ages 15 and 30, and Crohn's is most likely to begin between ages 20 and 29. The Lewis study also found that IBD is diagnosed less often in Black, Asian, and Hispanic Americans than in white Americans, although a 2023 *Lancet* review notes that IBD is becoming more common around the world.

Pediatric IBD

Pediatric IBD is inflammatory bowel disease that begins in childhood or the teen years, before adulthood. Riya, diagnosed at 14, is a pediatric case. Kids and teens face extra challenges because their bodies are still growing. NIDDK lists slowed growth, lower weight gain, and delayed puberty among possible complications of IBD in children, and long courses of steroids can also slow growth and weaken bones.

That is one reason pediatric care has changed. A 2026 study of 787 commercially insured US children newly diagnosed with Crohn's disease (Gonzalez and colleagues, *American Journal of Gastroenterology*) found that among children diagnosed in 2019 to 2023, 75% had started an advanced medicine, such as a biologic, within a year of diagnosis, a big increase over earlier years. This observational study shows a change in how doctors treat children, not proof that the change improves long-term outcomes.

IBD risk factors

So what causes IBD? Nobody knows exactly. **IBD risk factors** are the inherited and environmental factors that raise a person's chance of developing IBD without, on their own, causing it. Researchers think IBD develops when a person with a genetic tendency meets certain environmental exposures, and the immune system's relationship with gut microbes goes off track. Le Berre's 2023 review summarizes it this way for UC: genetic predisposition plus environmental exposures, with barrier defects, microbes, and a dysregulated immune response all strongly involved.

Here are the main risk factors with good human evidence:

- **Genes and family history.** IBD runs in families. NIDDK notes that having a parent or sibling with IBD raises a person's chance of developing it. In 2001, a team led by Jean-Pierre Hugot reported in *Nature* that variants in a gene called NOD2 were linked to Crohn's disease. NOD2 makes a protein that helps immune cells recognize bacterial parts, a clue that the problem involves how the immune system reads gut microbes. Many more gene regions have been found since, but each one raises risk only a little. Most people who carry a risk variant never get IBD.
- **Smoking.** NIDDK says research has shown smoking may double the chance of developing Crohn's disease.
- **The microbiome.** Studies find differences between the gut microbes of people with and without IBD (NIDDK). This is a correlation: inflammation itself and its treatments also change the microbiome, so scientists are still sorting out which comes first.

Notice what is *not* on that list as a proven cause: stress or "bad diet." Large studies have found some links worth investigating. For example, a 2021 study that followed more than 116,000 adults in 21 countries for about 10 years (Narula and colleagues, *BMJ*) found that people who ate more ultra-processed foods were more likely to be diagnosed with IBD later. That is a correlation, not proof of cause, and it says nothing about any one person. Stress and diet come up constantly online, and both deserve a Hype Meter check. (Need a refresher on how the grades work? See the Hype Meter.)

Hype Meter: "IBD is caused by stress"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. No good evidence shows that stress causes IBD to start; the causes involve genes, the immune system, gut microbes, and the environment. One large study of more than 150,000 US nurses found that women with recent depression symptoms were more likely to be diagnosed with Crohn's disease later (but not ulcerative colitis), an association that doesn't show cause (Ananthakrishnan and colleagues, 2013). A 2009 review by Singh, Graff, and Bernstein found strong evidence for an *association* between perceived stress and flares in people who already have IBD, and a weaker link with stressful life events. That is correlation, not cause: a flare can raise stress just as easily as stress might nudge a flare. **What would change the grade:** More large, long-term studies following healthy people before diagnosis, showing that stress consistently predicts who develops IBD after accounting for genes, smoking, and other factors, plus evidence of how it would work. Even then, "stress is one risk factor" would be very different from "stress causes IBD."

9.5 Flares and Remission

IBD rarely stays the same for long. It tends to come in waves.

A **disease flare** is a period when IBD becomes active, with increased inflammation and symptoms such as diarrhea, pain, bleeding, and tiredness. **Remission** is a period when IBD is quiet: symptoms fade or disappear, and ideally the inflammation settles too. NIDDK says periods of remission can last for weeks or years, and that the goal of treatment is to keep people in remission long term.

Think of it like the seasons in a dry forest. A flare is like a wildfire season, and remission is the quiet season in between. The quiet season is real and can last a long time, but the underlying conditions haven't vanished. Firefighters don't sell their trucks when the fires stop. In the same way, people with IBD usually keep taking maintenance medicine during remission, because it is the medicine that keeps the quiet season going. NIDDK says people with ulcerative colitis typically need lifelong treatment with medicines unless they have surgery to remove the colon and rectum.

Doctors distinguish clinical remission (the person feels well) from endoscopic healing (the gut lining looks healed on a camera exam). These don't always match: a person can feel fine while inflammation still simmers, which is why doctors keep checking (Section 9.7).

Flares can be set off by several things. Stopping or missing maintenance medicine is one. Gut infections can trigger symptoms, and the Singh review notes that some pain relievers called NSAIDs (such as ibuprofen) have been linked to flares, which is why NIDDK advises people with IBD to talk with their doctor before taking over-the-counter medicines. Often a flare has no obvious trigger at all, which is frustrating, and is nobody's fault.

Remission is not a reason to stop medicine on your own



Feeling great in remission is exactly what the medicine is supposed to do, not proof that you don't need it anymore. Any change to an IBD treatment plan is a decision to make with your care team, never on your own.

9.6 More Than the Gut: Extraintestinal Manifestations

IBD lives in the gut, but its effects don't stay there. An **extraintestinal manifestation** is a sign of IBD that shows up outside the intestines. ("Extra" means outside, and "intestinal" means the intestines.) NIDDK lists several:

- **Joints:** certain types of arthritis, with sore, swollen joints.
- **Skin:** rashes, including red, tender bumps under the skin.
- **Eyes:** redness, pain, or irritation.
- **Liver and bile ducts:** including a condition called primary sclerosing cholangitis (PSC).
- **Blood and bones:** anemia (too few red blood cells, which causes tiredness) and thinning bones, which can come from the disease and from long-term steroid use.
- **Growth:** slowed growth and delayed puberty in children.

An international expert group (the EXTRA consensus, published in 2022) noted that these manifestations happen frequently in IBD. They make sense once you remember that IBD is an immune disease. Immune cells and messenger molecules called cytokines (Chapter 4) travel in the blood, so inflammation that starts in the gut can affect tissues elsewhere.

The same idea explains effects on the brain, which we'll reach in Section 9.10.

9.7 Finding the Inflammation: Fecal Calprotectin and Colonoscopy

Belly pain and diarrhea can come from many conditions, including infections, IBS, and celiac disease. NIDDK describes the usual path to an IBD diagnosis: a medical and family history, a physical exam, and then blood tests, stool tests, endoscopy, and imaging.

The stool test: a smoke detector for gut inflammation

Riya's first clue came from a stool test. **Fecal calprotectin** is a protein released mainly by white blood cells called neutrophils that can be measured in stool; high levels signal inflammation in the intestines. When the gut wall is inflamed, neutrophils pour into it and some spill into the stool, carrying calprotectin with them. A 2019 review by Ricciuto and Griffiths explains that calprotectin levels rise in proportion to the degree of inflammation, which is why the test is useful for both screening and monitoring.

Think of fecal calprotectin as a smoke detector: it can tell you there is probably a fire somewhere in the intestines, but not where it is or what started it. A 2023 meta-analysis (Dajti and colleagues; 17 studies, 1,956 adults) found that the test correctly flagged about 86% of people who had IBD and correctly cleared about 92% of people who had IBS instead. All the included studies had high or unclear risk of bias, so the exact numbers are uncertain. A high result leads to the next step.

Colonoscopy: looking directly

Colonoscopy is a procedure in which a doctor passes a long, thin, flexible tube with a light and a tiny camera through the anus to look at the lining of the rectum and entire colon, and often the end of the small intestine, usually while the patient is sedated. NIDDK says endoscopy tests, which include colonoscopy, are the most accurate way to diagnose Crohn's disease. During the colonoscopy, the doctor takes biopsies: tiny pieces of the lining, painless to remove, that a pathologist examines under a microscope.

The doctor looks for the pattern of inflammation. Continuous inflammation starting at the rectum points to ulcerative colitis. Patchy inflammation with skip areas, especially at the end of the small intestine, points to Crohn's. Because Crohn's can affect parts of the small intestine a colonoscope can't reach, doctors may add imaging such as MRI, or a capsule endoscopy, where the patient swallows a pill-sized camera (NIDDK). For children and teens, the revised Porto criteria recommend both an upper endoscopy (a camera passed through the mouth to view the esophagus, stomach, and first part of the small intestine) and a colonoscopy for everyone suspected of having IBD, plus imaging of the small intestine unless the picture is clearly typical UC.

Here is how the two main tests compare.

	Fecal calprotectin	**Colonoscopy with biopsy**
What it is	Stool sample sent to a lab	Camera exam of the colon and end of the small intestine
What it tells you	Whether there is likely inflammation	Where the inflammation is, how severe, what type
Invasive?	No	Yes (bowel prep, sedation)
Main use	Screening and repeat monitoring	Diagnosis and checking for healing

Colonoscopy also has a long-term job. People who have had IBD in a large part of the colon for many years are more likely to develop colorectal cancer. NIDDK says people with long-standing ulcerative colitis that involves a third or more of the colon need closer screening, and that people with Crohn's disease in the large intestine may be advised to have screening colonoscopies to look for cancer or precancerous cells (called dysplasia). For Crohn's, NIDDK adds that the risk is higher the longer someone has had the disease, and in people who

also have PSC or a family history of colorectal cancer. These screening checks are a routine part of long-term IBD care.

9.8 The Treatment Toolbox

Treatment for IBD has two jobs: **induction** (calming an active flare) and **maintenance** (keeping remission going). NIDDK says medicines do not cure Crohn's disease, but they can reduce inflammation and bring on and maintain remission. Doctors choose based on the type of IBD, where it is, how severe it is, and the person's age.

So many drug names



The drug names in this section are a mouthful, and you don't need to memorize them. Focus on the *job* each class does, and which part of the immune alarm system it turns down.

Here are the main classes, from oldest to newest.

Aminosalicylate. An **aminosalicylate** (also called a 5-ASA drug) is an anti-inflammatory medicine, such as mesalamine or sulfasalazine, that works on the lining of the gut and is used mainly for mild to moderate ulcerative colitis. NIDDK says doctors prescribe them to treat mild or moderate UC or to help people stay in remission. They are long-established older medicines. They are not a standard treatment for Crohn's disease.

Corticosteroid. A **corticosteroid** (often just called a steroid) is a powerful, fast-acting medicine related to the body's stress hormone cortisol that broadly calms the immune system. Examples include prednisone and budesonide; they are lab-made, much stronger relatives of the cortisol you met in Chapter 7. A 2021 *JAMA* review by Cushing and Higgins describes steroids giving rapid symptom relief while longer-term therapy gets started, which is why Riya got a course at diagnosis. NIDDK warns that steroids should be used only short term, because long-term use can cause serious side effects, including bone thinning. Steroids are a bridge, not a destination.

Immunomodulator. An **immunomodulator** is a medicine that dampens the immune system's activity more slowly and steadily, used mainly to maintain remission or to help other medicines work better. Examples include azathioprine, 6-mercaptopurine (together called thiopurines), and methotrexate. They are long-established and take weeks to months to work fully.

Biologic therapy. Biologic therapy is treatment with a medicine made by living cells, usually a lab-made antibody, that blocks one specific immune signal or cell pathway involved in inflammation. Instead of turning down the whole immune system, a biologic is like cutting one specific wire in the alarm system. Biologics are given by injection or by infusion into a vein; Riya takes one by injection. Different biologics block different targets:

- **Anti-TNF therapy** is a type of biologic treatment that blocks tumor necrosis factor (TNF), a cytokine that drives inflammation in IBD. Infliximab and adalimumab are examples. Anti-TNF medicines were the first biologics approved for IBD.
- **Anti-integrin therapy** (vedolizumab) blocks a molecule that immune cells use to enter the gut, so fewer inflammatory cells reach the gut wall.
- **Anti-interleukin therapies** block other cytokines called interleukins. Ustekinumab blocks interleukins 12 and 23; risankizumab, mirikizumab, and guselkumab block interleukin 23.

JAK inhibitor. A **JAK inhibitor** is a pill, a small molecule rather than an antibody, that blocks Janus kinase (JAK) enzymes inside immune cells, which relay signals from many cytokines at once. Tofacitinib and upadacitinib are examples. Another class of pills, called S1P receptor modulators (ozanimod and etrasimod), keeps certain immune cells trapped in lymph nodes so fewer reach the gut. The S1P modulators are approved for UC but not for Crohn's disease.

The table below shows when the US Food and Drug Administration (FDA) first approved some of these medicines specifically for ulcerative colitis or Crohn's disease in adults. Many were approved earlier for other diseases; the years here are for IBD.

Medicine (class)	First FDA approval for UC	First FDA approval for Crohn's
Infliximab (anti-TNF)	2005	1998
Adalimumab (anti-TNF)	2012	2007
Vedolizumab (anti-integrin)	2014	2014
Ustekinumab (anti-IL-12/23)	2019	2016
Tofacitinib (JAK inhibitor)	2018	Not approved for Crohn's
Ozanimod (S1P modulator)	2021	Not approved for Crohn's
Upadacitinib (JAK inhibitor)	2022	2023
Risankizumab (anti-IL-23)	2024	2022
Mirikizumab (anti-IL-23)	2023	2025
Guselkumab (anti-IL-23)	2024	2025

New medicines keep arriving, including for children. In April 2026, the FDA approved ustekinumab for moderately to severely active Crohn's disease in children aged 2 and older, and later in 2026 for ulcerative colitis in the same age group. Other drugs are still experimental. For example, an oral drug called obefazimod is being tested for UC, but as of October 2026 it is **not** FDA approved; its maker said in July 2026 that it planned to submit an application by the end of the year.

Food as treatment: exclusive enteral nutrition

For children with Crohn's disease, a liquid formula can be a real medical treatment. In **exclusive enteral nutrition** (EEN), a child drinks a nutritionally complete formula, and usually nothing else, for a set number of weeks under a care team's supervision. The newest guideline on pediatric Crohn's disease from two European expert groups (ECCO and ESPGHAN), published in 2026, names two preferred ways to induce remission in children with lower-risk Crohn's disease in the bowel: EEN, or the Crohn's Disease Exclusion Diet combined with partial enteral nutrition (a structured list of allowed foods plus formula for part of each day). For children at high risk of a complicated course, the same guideline recommends starting an anti-TNF biologic as the first treatment. Both nutrition therapies are supervised medical treatments with a defined plan, not lifestyle diets, and long-term care still aims for a healed lining and normal growth.

Hype Meter: "Diet alone can cure Crohn's disease"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. No diet has been shown to cure Crohn's disease. The real finding is narrower: the 2026 ECCO-ESPGHAN guideline update prefers exclusive enteral nutrition (a supervised liquid-formula treatment), or a structured exclusion diet combined with partial formula, to induce remission in children with lower-risk Crohn's. Inducing remission is not curing, and a nutrition therapy planned and monitored by a care team is not a diet plan sold online. **What would change the grade:** Long-term randomized trials showing that a specific diet keeps people in lasting remission with a healed lining, without medicine, would make a narrower claim worth grading. "Cure" would require the disease to stay gone for good.

IBD surgery

IBD surgery is an operation to remove a severely diseased section of bowel or to treat a complication of IBD, such as a stricture, fistula, abscess, severe bleeding, or precancerous changes. The two types of IBD lead to different kinds of surgery:

- **In ulcerative colitis,** surgeons usually remove the colon and rectum. Because UC lives only there, this removes the disease from the gut. NIDDK describes two common options: an internal pouch made from the end of the small intestine and connected to the anus (so stool still leaves the usual way), or an ileostomy, an opening on the belly called a stoma where stool collects in a pouch. The Le Berre review says 10% to 20% of people with UC still need this surgery despite modern medicines.

- **In Crohn's disease,** surgeons remove only the damaged section and reconnect the healthy ends (a resection). NIDDK notes surgery won't cure Crohn's, because it can come back elsewhere. The Cushing and Higgins review says more than half of people with Crohn's eventually develop complications that need surgery.

Surgery is not a failure. For many people, it is the step that gives them their life back.

9.9 Treat to Target: Mucosal Healing

For a long time, the goal of IBD treatment was simple: make the symptoms go away. Doctors now aim higher.

Mucosal healing is the healing of the gut's inner lining (the mucosa), so that ulcers and visible inflammation are gone when doctors look with an endoscope. It is also called endoscopic healing. Why does it matter if you already feel fine? Because inflammation that keeps simmering under the surface can slowly damage the bowel, leading to strictures, fistulas, and surgery, especially in Crohn's.

An international group of IBD experts, the International Organization for the Study of IBD, published targets called STRIDE-II in 2021. Based on a review of 435 studies and voting by experts, STRIDE-II set short-term targets of symptom relief and normal blood and stool markers, such as calprotectin. Its long-term targets are clinical remission and endoscopic healing, plus the absence of disability, a restored quality of life, and normal growth in children. This approach is called "treat to target." If the stool test or colonoscopy shows inflammation is still there, the care team may adjust treatment even if the person feels well.

European pediatric guidelines make the same point for children. The 2020 ECCO-ESPGHAN guideline said repeated calprotectin tests or bowel imaging are more reliable ways to track treatment response than symptom scores alone, and its 2026 update lists endoscopic remission, normal growth, and a good quality of life as long-term goals.

9.10 IBD and the Brain

Now we reach the gut-brain part of the story. People with IBD often describe low energy, worry, or sadness that comes with a flare. Is that the stress of being sick, or does gut inflammation change the brain? Probably both, with arrows in both directions.

How common are anxiety and depression in IBD?

In 2021, Barberio and colleagues combined data from 77 studies of 30,118 adults with IBD. They found that about 32.1% had symptoms of anxiety and about 25.2% had symptoms of depression, roughly 1 in 3 and 1 in 4. During active disease, the numbers were higher: anxiety symptoms in 57.6% (compared with 38.1% in inactive disease) and depression symptoms in 38.9% (compared with 24.2%). These were scores on screening questionnaires, not clinical diagnoses.

How to read a gut-brain claim: the 2021 IBD anxiety and depression meta-analysis

Question	This study
Mouse or human?	Human. Adults with IBD (studies had to include at least 100 adult patients).
Correlation or cause?	Correlation. It pooled observational studies that measured symptoms at one time. It can't show whether IBD causes anxiety, anxiety worsens IBD, or both.
How many?	Very large: 77 studies with 30,118 patients in total. But the studies differed a lot from each other, so the pooled numbers are averages across very different groups.
How long?	Mostly snapshots. Each study measured symptoms at one point, so it can't show how mood changes over time in one person.
Who paid for it?	The paper states that the study received no specific funding.
Is something being sold?	No. The authors' message was that gut doctors should screen for and treat anxiety and depression.

The conclusion: anxiety and depression symptoms are common in IBD, especially during flares. What the study can't tell us is why. The jump in depression symptoms from inactive to active disease fits the idea that inflammation affects mood, but it also fits the idea that feeling sick and missing school lower mood. Both are likely true at once.

Possible pathways from gut to brain

Here are the main routes scientists are studying, building on earlier chapters:

1. **Cytokines.** Inflammatory cytokines can signal the brain and trigger "sickness behavior" such as tiredness, poor sleep, and low mood (Chapter 4).
2. **The vagus nerve.** Vee's home nerve carries sensory information from the gut to the brainstem (Chapter 2). It also carries signals back down. A 2016 paper by Bruno Bonaz and colleagues describes the vagus nerve as having anti-inflammatory effects, both through the HPA axis and through a pathway that calms immune cells in the gut.
3. **Pain and sensitization.** Repeated pain during flares can make the nervous system more sensitive (Chapter 8).

4. **Life stress.** Living with an unpredictable illness is stressful, and stress changes how the gut feels and functions (Chapter 7). NIDDK notes that stress may change the gut microbiome in ways that can worsen Crohn's symptoms.

Because the vagus nerve can calm inflammation, some researchers have asked whether stimulating it with an implanted device could treat Crohn's. This idea gets shared online more confidently than the evidence allows.

Hype Meter: "Vagus nerve stimulation can treat Crohn's disease"

Strong	Moderate	**Preliminary**	Hype

Verdict: Preliminary. Bonaz and colleagues had shown that vagus nerve stimulation improved colitis in rats. In a 2016 pilot study, they implanted stimulators in 7 people with active Crohn's disease and followed them for 6 months. Two were removed from the study at 3 months because they got worse; five reached remission. With only 7 people and no comparison group, the study shows the approach is feasible, not that it works. Implanted vagus nerve stimulators are FDA approved for some other conditions, but **not** for Crohn's disease. **What would change the grade:** Larger randomized trials comparing real stimulation with sham (fake) stimulation in people with Crohn's, measuring both symptoms and healing of the gut lining.

Care for the whole person

Because mood and IBD are so tangled, the Barberio authors recommended that gut doctors screen for and treat anxiety and depression, and the Dolinger review includes a psychosocial assessment (a check on mood, stress, and daily life) in a complete evaluation. Treating anxiety or depression won't replace IBD medicine, but it can make living with IBD more manageable. Chapter 11 goes deeper.

If you're going through this

If you have IBD and feel anxious before flares or low during them, you're not weak and you're not imagining it. Mood changes are common in IBD, and they're worth bringing up with your care team just like a new symptom. Many teens find it helps to have a school plan with restroom access, arranged through the nurse or counselor, and one friend who knows. You can also ask your doctor about talking with a psychologist who works with people with IBD.

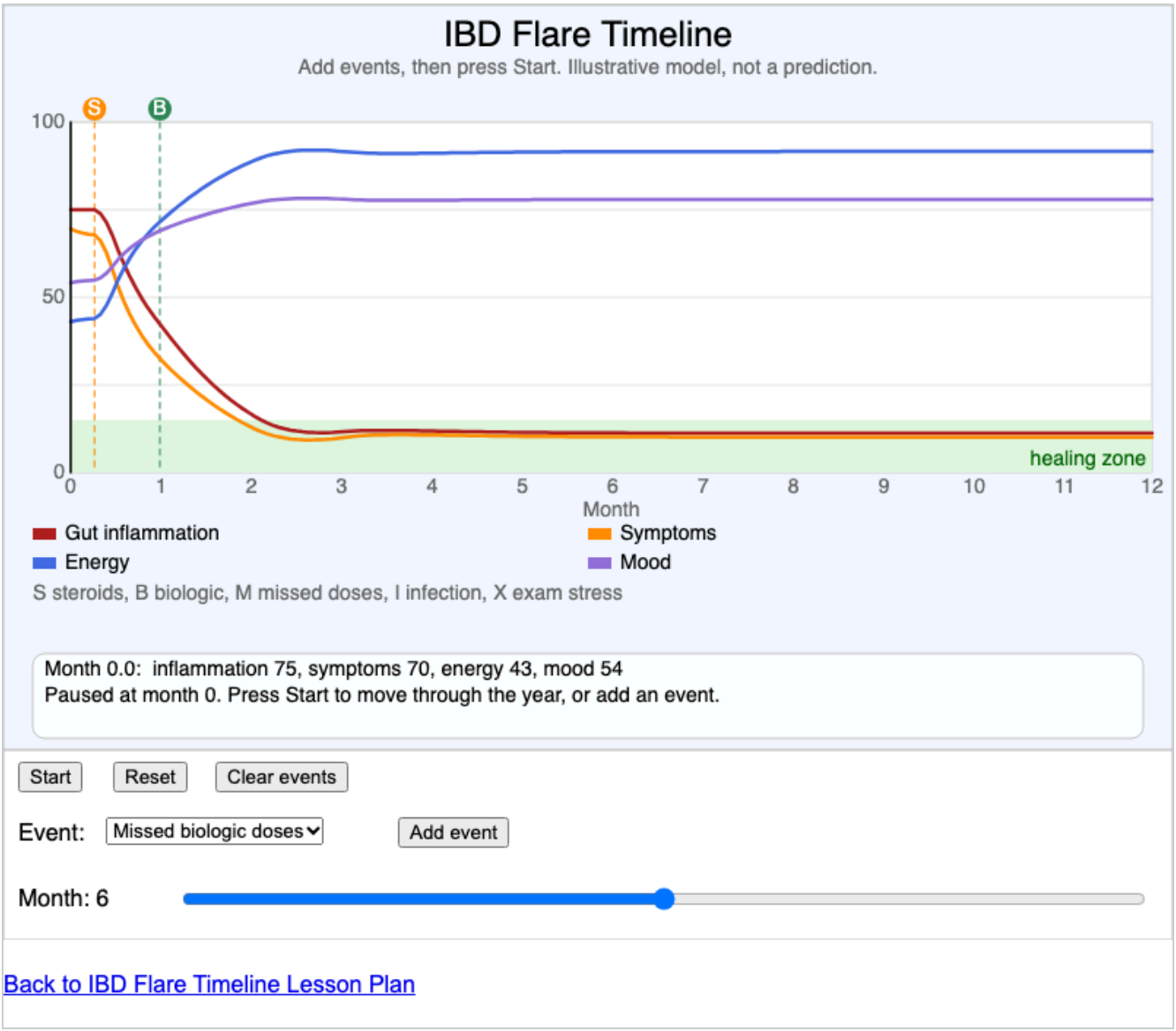
For families

Parents often wonder whether something they did, fed, or allowed caused their child's IBD. It didn't: IBD comes from a mix of genes, the immune system, gut microbes, and environment, and no family causes it. Helpful things to say sound like "That sounds really hard" or "What would help today?" Less helpful are "Are you sure you need the bathroom again?" or "Have you tried cutting out sugar?" If your child's medicine is hard to afford or keep up with, tell the care team, because there are often ways to help, and missed doses can lead to flares.

9.11 Seeing the Year at Once: The IBD Flare Timeline

You now know the pieces: inflammation, symptoms, flares and remission, medicines that work on different time scales, and the gut-brain links to energy and mood. The MicroSim below puts them together on one chart. Each curve runs from 0 to 100 in made-up units. "Inflammation" stands for the immune attack in the gut wall, "symptoms" for pain, diarrhea, and urgency, and the green "healing zone" for inflammation low enough that the lining can heal.

Diagram: IBD Flare Timeline



Back to IBD Flare Timeline Lesson Plan

Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch09-ibd-flare-timeline/main.html

Open the IBD Flare Timeline fullscreen

MicroSim specification: IBD Flare Timeline

Type: microsim **sim-id:** ch09-ibd-flare-timeline
Library: p5.js
Status: Implemented
Bloom Level: Analyze
Bloom Verb: relate, analyze
Learning Objective: The learner will relate gut inflammation, symptoms, energy, and mood over 12 months in Crohn's disease and analyze how treatment events (steroids, a biologic, missed doses) and other events (an infection, a stressful exam week) change each curve on a different time scale.

Canvas: 510 px drawing area plus 130 px controls (iframe 642 px); responsive to about 380 px wide.

Controls: Start/Pause (moves a playhead through the year), Reset, Clear events; Event select (Start steroids, Start biologic, Missed biologic doses, Gut infection, Stressful exam week) with an Add event button; Month slider (0 to 12, step 0.5).

Rules: Starts with active disease. Steroids act within about a week and taper off by 12 weeks, lowering symptoms faster than inflammation. A biologic builds up over weeks and holds inflammation low; missed doses (45 days) let its effect fade, and inflammation returns over weeks. An infection adds a short spike. Exam stress raises symptoms and lowers mood for about two weeks but does not change inflammation.

Feedback: A readout gives the month and all four values at the playhead, plus a note explaining the most recent event.

Provenance: Steroids as a short-term bridge and biologics for maintenance (NIDDK; Cushing and Higgins 2021); mood worse in active disease (Barberio 2021); stress and flares associated but cause unclear (Singh 2009). All numbers are illustrative.

Start with the default plan (steroids, then a biologic at month 1) and press Start. In the first two months, the orange symptom curve drops faster than the red inflammation curve. That gap is why someone can feel better before their gut has healed, and why doctors check calprotectin or look with a scope instead of relying on symptoms alone.

Now choose **Missed biologic doses**, set the month to 6, and add it. Inflammation doesn't jump the next day; it creeps back over weeks, and symptoms, energy, and mood follow. Then add a **Stressful exam week** at month 10. Symptoms and mood change, but the red inflammation line doesn't move. That was a deliberate choice: the evidence links stress with how people feel, but it doesn't show that stress drives gut inflammation. Finally, press **Clear events** to see a year with no treatment.

What this model leaves out

- Real IBD is far less predictable. Flares often happen with no clear trigger, and two people on the same medicine can respond very differently.
- The model has one inflammation number, but real inflammation differs by location, depth, and type (UC versus Crohn's), and complications like strictures don't heal the same way.
- Medicine timing is simplified. Real drugs differ in how fast they work, some stop working over time, and side effects aren't shown.
- Mood depends on far more than gut symptoms: sleep, friends, school, family, and mental health care all matter, and mood can affect symptoms too.
- All numbers are made up for teaching. This is not a prediction for any real person.

At the Bedside: Riya's Story, From Diagnosis to Remission

Meet the patient (fictional)

Riya is 14 and in the spring of eighth grade. For about six months she has had cramping pain in her lower right belly, diarrhea several times a day, and a tiredness that sleep doesn't fix. She has lost weight without trying and has stopped finishing meals. Her parents notice she has quit practicing violin and goes to bed early.

What the doctor checks: Dr. Alvarez asks how long the symptoms have lasted, about blood in the stool, nighttime symptoms, joint pain, rashes, and family history, and checks Riya's growth chart. Blood tests show mild anemia and signs of inflammation. A stool test rules out infection and shows a high fecal calprotectin. Next come an upper endoscopy and a colonoscopy, both with biopsies, and an MRI of the small intestine.

Connecting the signals: Months of diarrhea, weight loss, and fatigue with a high calprotectin point to real inflammation, not a disorder of gut-brain interaction like IBS. The colonoscopy shows patchy ulcers with healthy skip areas in the end of the small intestine and part of the colon, the biopsies show inflammation typical of Crohn's, and the MRI shows thickening through the bowel wall, a sign of transmural inflammation.

Diagnosis: Crohn's disease affecting the end of the small intestine and part of the colon (pediatric IBD).

Why it happens: Riya likely inherited some genetic tendency toward IBD, and her gut immune system began overreacting to her gut microbes and lining instead of settling down. Nothing she ate or felt caused it.

The mind-body side: Riya's mood had dropped well before diagnosis, partly from feeling sick and embarrassed and perhaps partly from inflammatory signals reaching her brain (Section 9.10). She also began worrying that a flare might start during an orchestra concert. Dr. Alvarez's team screens her for anxiety and depression and connects her with the clinic psychologist, who teaches coping skills for pre-flare worry. The school nurse sets up a plan for restroom access and missed work.

Treatment today: Because Riya's symptoms were moderate and she was losing weight, Dr. Alvarez talked with the family about two ways to calm the flare quickly: exclusive enteral nutrition, which European pediatric guidelines prefer for children with lower-risk disease, or a short course of steroids. They chose steroids, with a careful taper, and Dr. Alvarez planned a biologic medicine by injection for long-term maintenance. (Care teams weigh these choices for each child; neither is right for everyone.) Within weeks Riya felt better, and within a few months her calprotectin came down. A follow-up check showed her lining healing, which is the goal of "treat to target." Now 16, she is mostly in remission and keeps taking her biologic, with occasional flares that her care team manages. She is back to violin and cooking with her grandmother.

What's new in research: Pediatric care is moving toward advanced medicines earlier. A 2026 study of 787 US children with newly diagnosed Crohn's disease found that 75% of those diagnosed in 2019 to 2023 started an advanced therapy, such as a biologic, within a year (Gonzalez et al., *American Journal of Gastroenterology*, 2026). **Evidence grade: Moderate.** It is a large observational study of insurance records from commercially insured children. It shows a clear change in practice, but it couldn't confirm whether earlier treatment lowered the need for surgery, so randomized and longer studies are still needed.

Your turn: reason through a variation

Suppose a 15-year-old named Kenji has had diarrhea with visible blood for two months, an urgent need to go, and cramping, but no weight loss. His calprotectin is high, and his colonoscopy shows continuous inflammation starting at the rectum and extending partway up the colon, limited to the inner lining, with no skip areas and a normal small intestine. Which type of IBD fits best, and how is his likely treatment different from Riya's?

Answer: The continuous pattern starting at the rectum, limited to the inner layers and to the colon, plus bloody diarrhea, fits ulcerative colitis rather than Crohn's disease. For mild to moderate UC, doctors often start with an aminosalicylate, which is not a standard treatment for Crohn's, and add steroids or advanced medicines if needed. If UC ever became severe and didn't respond to medicine, removing the colon and rectum would remove the disease from his gut, which isn't true for Crohn's.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: IBD and IBS are the same thing with slightly different names.
Reality: IBD (Crohn's disease and ulcerative colitis) involves visible, measurable inflammation and damage in the gut wall, found on tests like fecal calprotectin and colonoscopy. IBS is a disorder of gut-brain interaction in which the gut looks normal on these tests. They are treated very differently (see Chapter 10).

Myth: IBD is caused by stress or a bad diet.
Reality: IBD develops from a combination of genes, an overactive immune response, gut microbes, and environmental factors such as smoking. Perceived stress is associated with flares in people who already have IBD, and some large studies link depression symptoms or eating patterns with a higher later risk, but these are

correlations. No good evidence shows that stress or diet by itself starts the disease, and nobody causes their own IBD.

Myth: IBD only affects the gut.
Reality: IBD can cause extraintestinal manifestations in the joints, skin, eyes, liver, blood, and bones, and can slow growth in children. Anxiety and depression symptoms are also common, especially during active disease.

Myth: Once you are in remission, you can stop your treatment.
Reality: Maintenance medicine is usually what keeps remission going, and NIDDK says people with ulcerative colitis typically need lifelong treatment unless their colon and rectum are removed. Any change in treatment should be decided with a doctor.

Myth: If you feel fine, your gut must be healed.
Reality: Symptoms can improve before inflammation is gone. That's why care teams track calprotectin and check the lining directly, aiming for mucosal healing, not just feeling better.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "I healed my Crohn's in 30 days with this gut-reset cleanse. Doctors just want to keep you on drugs! Link in bio."

Grade: Hype. No cleanse or diet has been shown to cure Crohn's disease, and one person's story can't separate the cleanse from a natural period of remission, which can happen on its own. The real evidence for nutrition is narrower: supervised exclusive enteral nutrition can induce remission in some children with Crohn's, and it is followed by maintenance medicine. The "link in bio" means something is being sold. A careful version would say: "Some nutrition therapies, prescribed by a care team, can help induce remission in certain children with Crohn's, but they are not a cure."

2. Predict: Riya goes to a month-long summer music camp and forgets to bring her biologic, so she misses two doses. She feels fine for the first couple of weeks. What would you predict, and why?

Feeling fine at first fits how biologics work: their effect fades gradually. Over the following weeks, as the medicine level drops, the immune signal it blocked can return, so inflammation may creep up, followed by symptoms, tiredness, and lower mood, as in the IBD Flare Timeline. The right move is to contact Dr. Alvarez's team as soon as she realizes, rather than waiting for symptoms.

3. Explain: At a check-up, Riya says she feels great, but her fecal calprotectin is higher than last time. Explain how both can be true and why her doctor cares.

Calprotectin comes from neutrophils that move into an inflamed gut wall, so a higher level suggests inflammation is increasing, even if it isn't yet causing symptoms. Symptoms often lag behind inflammation or don't match it closely. Her doctor cares because the treatment target is a healed lining, not just feeling well, and simmering inflammation in Crohn's can slowly lead to complications like strictures. The doctor might repeat the test, order imaging or a colonoscopy, or adjust treatment.

4. Apply: A 17-year-old with ulcerative colitis has had painful, swollen knees and red, sore eyes during his last two flares. His friend says, "That can't be related to your gut." Use this chapter to respond.

Both can be extraintestinal manifestations of IBD. NIDDK lists certain types of arthritis and eye irritation among the effects of UC outside the gut. They make sense because IBD is an immune-mediated disease: inflammatory cells and cytokines travel in the blood, so inflammation that starts in the gut can affect other tissues. He should tell his care team, because these problems may need their own treatment and may also signal disease activity.

5. Read the data. Three US studies estimated how many people have IBD, using different methods:

Study	Method	Who was counted	Result
Lewis et al. 2023	Insurance claims (diagnosis and treatment records)	All ages	About 721 per 100,000 (about 0.7%), roughly 2.39 million people
Kappelman et al. 2025	Insurance claims	Under age 20	About 122 per 100,000, roughly 100,000 young people
NCHS 2026 (survey years 2023 to 2024)	National survey: "Has a doctor ever told you...?"	Adults 18 and older	1.6% of adults, about 4.1 million

5. What does this data show, and what can't it show?

It shows that IBD is far from rare, with millions of Americans affected, including about 100,000 people under 20. It also shows that the method changes the answer: the adult survey (1.6%) is more than twice the claims estimate (about 0.7%), probably because a survey counts anyone ever told they had IBD, including mistaken diagnoses. These numbers can't show what causes IBD or whether it is increasing, since the methods and time periods differ. A helpful follow-up would track one population with the same method over many years.

Exercises

Remember

1. Name the two main types of inflammatory bowel disease and state where in the digestive tract each one can occur.

Answer

Ulcerative colitis affects only the colon and rectum. Crohn's disease can affect any part of the digestive tract, from the mouth to the anus, most often the end of the small intestine and the start of the colon.

1. What does a high fecal calprotectin result suggest, and which cells release calprotectin?

Answer

It suggests inflammation in the intestines. Calprotectin comes mainly from neutrophils, a type of white blood cell that moves into inflamed gut tissue.

Understand

1. Explain why transmural inflammation in Crohn's disease can lead to strictures and fistulas, while ulcerative colitis usually doesn't.

Answer

Transmural inflammation goes through the whole thickness of the gut wall. Deep inflammation can scar and narrow the bowel (strictures) or eat through the wall and form tunnels to other organs or the skin (fistulas). Ulcerative colitis usually stays in the inner layers, so it rarely causes these deep complications.

1. Explain the difference between how a corticosteroid and a biologic therapy calm inflammation, and why steroids are used only short term.

Answer

A corticosteroid broadly turns down much of the immune system and works quickly, so it calms a flare fast. A biologic blocks one specific immune signal, such as TNF, and is used for long-term maintenance. Steroids are used only short term because long-term use can cause serious side effects, such as bone thinning, and they aren't meant to maintain remission.

Apply

1. Use the IBD Flare Timeline. Run the default plan and record the month when symptoms first fall below 25 and the month when inflammation first enters the healing zone. Then explain what that gap means for how doctors decide whether treatment is working.
2. A friend with Crohn's disease tells you she's thinking of skipping her next injection because she has felt great for six months. Using what you learned about remission, maintenance, and mucosal healing, write two or three supportive sentences you could say that encourage her to talk with her care team, without giving medical advice yourself.

Analyze

1. Compare the claims-data estimate (about 0.7% of Americans) with the survey estimate (1.6% of adults) for IBD. Identify at least two reasons they differ, and explain which number is better for answering "How many Americans are living with diagnosed IBD?"
2. In the Barberio 2021 meta-analysis, depression symptoms were more common in active IBD (38.9%) than in inactive IBD (24.2%). Analyze at least three different explanations for this difference, including at least one gut-to-brain pathway and one that does not involve inflammation acting on the brain.

Evaluate

1. A news headline reads: "Stress triggers Crohn's flares, study finds." Using the Singh 2009 review and the Hype Meter, evaluate whether the headline is fair. Write a more accurate headline of 15 words or fewer.
2. Some experts argue that children with Crohn's should start a biologic soon after diagnosis; others prefer to start with milder treatments and move up only if needed. Using evidence from this chapter (pediatric growth, the Gonzalez 2026 study, the 2026 ECCO-ESPGHAN guideline update, and treat-to-target goals), evaluate the strengths and weaknesses of each approach. What evidence would settle the question?

Create

1. Design a one-page "IBD at school" guide for teachers that explains, in plain language, what IBD is, what a flare looks like, and three specific accommodations that could help a student like Riya. Make sure it doesn't blame the student or suggest diet or stress caused the disease.
2. Design a study to test whether a 12-week anxiety-coping program improves quality of life in teens with Crohn's disease. Describe the groups, how you would assign teens to them, what you would measure (include at least one measure of inflammation and one of mood), and how long you would follow them.

Key Takeaways

- Inflammatory bowel disease is an immune-mediated disease: the body's own immune response causes long-lasting, recurring gut inflammation. It has no cure, but treatment can keep people in remission for long periods.
- Ulcerative colitis affects only the colon and rectum, continuously and in the inner layers. Crohn's disease can affect any part of the gut, in patches, with transmural inflammation that can cause strictures, fistulas, and abscesses.
- About 2.4 million Americans, including about 100,000 people under 20, have diagnosed IBD (claims data); surveys give higher numbers because they measure something different. Risk comes from genes, the immune system, gut microbes, and environment, such as smoking. Stress and diet have not been shown to cause it.
- Fecal calprotectin acts like a smoke detector for gut inflammation, and colonoscopy with biopsy shows where the inflammation is and what type it is.
- Treatment classes include aminosalicylates, corticosteroids (a short-term bridge), immunomodulators, biologic therapies such as anti-TNF medicines, and JAK inhibitors, plus exclusive enteral nutrition in children and IBD surgery when needed. Maintenance treatment usually continues during remission.
- The modern goal is mucosal healing, a healed gut lining, not just fewer symptoms, because symptoms can improve before inflammation is gone.
- IBD affects the whole person: extraintestinal manifestations are common, and so are anxiety and depression symptoms, especially during flares.

You followed Riya from diagnosis to remission!



You can now explain what's happening inside a gut with IBD, how doctors find it and treat it, and why mood belongs in the conversation. Next, in Chapter 10, we meet Sam, whose tests all came back normal, and discover why "normal tests" doesn't mean "nothing is wrong."

Quiz: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's

Test your understanding of Chapter 9. Choose the best answer, then click **Show Answer** to check.

Question 1

Which statement correctly describes where ulcerative colitis occurs?

A. Anywhere from the mouth to the anus, in patches

B. Only in the colon and rectum, continuously from the rectum upward

C. Only in the small intestine, through the whole thickness of the wall

D. Only in the stomach and the first part of the small intestine

Show Answer

The correct answer is **B**. Ulcerative colitis affects only the colon and rectum, starting at the rectum and spreading upward in one continuous stretch, in the inner layers of the wall. Option A describes Crohn's disease, which is the most common mix-up.

Concept Tested: Ulcerative Colitis **Bloom's Level:** Remember

---

Question 2

What does "transmural inflammation" mean?

A. Inflammation that moves from one person to another

B. Inflammation that affects only the inner lining of the colon

C. Inflammation that appears outside the gut, such as in the joints

D. Inflammation that extends through the entire thickness of the gut wall

Show Answer

The correct answer is **D**. "Trans" means across and "mural" means wall, so transmural inflammation goes through every layer of the gut wall. It is typical of Crohn's disease. Option C describes an extraintestinal manifestation, a different idea.

Concept Tested: Transmural Inflammation **Bloom's Level:** Remember

---

Question 3

Fecal calprotectin is a useful test because it:

A. Comes mainly from neutrophils that move into inflamed gut tissue, so high stool levels signal intestinal inflammation

B. Shows exactly which part of the intestine is inflamed

C. Measures how many bacteria live in the colon

D. Confirms a diagnosis of Crohn's disease without any other tests

Show Answer

The correct answer is **A**. Calprotectin is released mainly by neutrophils, and its level in stool rises with intestinal inflammation. Like a smoke detector, it signals that inflammation is probably present but can't show where it is or what type it is (options B and D), which is why colonoscopy with biopsy is still needed.

Concept Tested: Fecal Calprotectin **Bloom's Level:** Remember

---

Question 4

Why do doctors use corticosteroids only as a short-term treatment in IBD?

A. They take many months to start working

B. They work only in ulcerative colitis, not Crohn's disease

C. They act fast to calm inflammation, but long-term use can cause serious side effects such as bone thinning

D. They cure IBD after one course, so longer use is unnecessary

Show Answer

The correct answer is **C**. Steroids broadly calm the immune system and relieve symptoms quickly, which makes them a good bridge while longer-term medicine starts working. Long-term use can cause serious side effects, so they are not used to maintain remission. Option D is wrong because no medicine cures IBD.

Concept Tested: Corticosteroid **Bloom's Level:** Understand

Question 5

How does a biologic therapy such as an anti-TNF medicine differ from a corticosteroid?

A. A biologic blocks one specific immune signal, while a steroid broadly turns down much of the immune system

B. A biologic is a pill, while a steroid must be injected

C. A biologic is used only during flares, while a steroid is used for long-term maintenance

D. A biologic kills gut bacteria, while a steroid repairs the gut lining

Show Answer

The correct answer is **A**. An anti-TNF biologic is a lab-made antibody that blocks one cytokine, tumor necrosis factor, while steroids act broadly. Option C reverses their usual roles: steroids are the short-term bridge, and biologics are commonly used for maintenance.

Concept Tested: Biologic Therapy **Bloom's Level:** Understand

---

Question 6

Why is mucosal healing, not just symptom relief, a long-term treatment target in IBD?

A. Because symptoms in IBD are imaginary and can't be measured

B. Because mucosal healing means the disease is cured

C. Because a healed lining means medicine can always be stopped

D. Because symptoms can improve while inflammation keeps simmering and slowly damaging the bowel

Show Answer

The correct answer is **D**. Symptoms and inflammation don't always match, so a person can feel well while inflammation continues, which in Crohn's can lead to strictures and fistulas. STRIDE-II therefore set endoscopic healing as a long-term target. Option B is wrong because healing is a sign of good control, not a cure.

Concept Tested: Mucosal Healing **Bloom's Level:** Understand

---

Question 7

A 16-year-old has had bloody diarrhea and urgency for two months. Colonoscopy shows continuous inflammation from the rectum partway up the colon, limited to the inner lining, and a normal small intestine. Which diagnosis fits best?

A. Crohn's disease

B. Ulcerative colitis

C. Irritable bowel syndrome

D. Hirschsprung disease

Show Answer

The correct answer is **B**. Continuous inflammation starting at the rectum, limited to the colon and the inner layers, with bloody diarrhea, is the pattern of ulcerative colitis. Crohn's (option A) would usually show patchy, transmural inflammation, often in the end of the small intestine. IBS (option C) would not show visible inflammation.

Concept Tested: Ulcerative Colitis **Bloom's Level:** Apply

Question 8

Riya has felt well for months on her biologic. A classmate says, "You're in remission, so you can stop your shots now." Based on the chapter, what is the best response?

A. "You're right, remission means the disease is gone."

B. "I'll stop for a month and see what happens."

C. "Maintenance medicine is usually what keeps remission going, so any change is a decision for my care team."

D. "Remission only happens in ulcerative colitis, so it doesn't apply to me."

Show Answer

The correct answer is **C**. Remission is a quiet period, not a cure, and maintenance medicine usually keeps it going. Stopping on your own (option B) can let inflammation return weeks later, as the IBD Flare Timeline shows. Remission happens in both Crohn's and UC, so option D is false.

Concept Tested: Remission **Bloom's Level:** Apply

Question 9

In a 2021 meta-analysis of 30,118 adults with IBD, depression symptoms were found in 38.9% of people with active disease and 24.2% of people with inactive disease. Which conclusion is best supported?

A. Depression symptoms are more common during active IBD, but this study can't show which causes which

B. Gut inflammation has been proven to cause depression

C. Depression causes IBD flares

D. Treating depression cures IBD

Show Answer

The correct answer is **A**. The studies were observational snapshots using symptom questionnaires, so they show an association. Inflammation might affect mood, feeling sick might lower mood, or mood might affect symptoms. Options B and C each claim one direction of cause that this design can't establish.

Concept Tested: Disease Flare **Bloom's Level:** Analyze

Question 10

A survey found that 1.6% of US adults say a doctor told them they had IBD, while insurance claims data put IBD at about 0.7% of Americans. What best explains the difference?

A. IBD became twice as common in the time between the two studies

B. One of the studies must have made an arithmetic mistake

C. Claims data count only children, so they miss most adults

D. The survey counts anyone ever told they had IBD, which can include old or mistaken diagnoses, while claims require actual diagnosis and treatment records

Show Answer

The correct answer is **D**. The two methods measure different things: self-report of ever being told versus records of diagnosis and treatment. Option A is tempting, but different methods can't show a trend, and the claims estimate covers all ages, so option C is wrong too.

Concept Tested: Inflammatory Bowel Disease **Bloom's Level:** Analyze

Chapter 10: IBS and Disorders of Gut-Brain Interaction

Summary

Irritable bowel syndrome (IBS) causes real, recurring belly pain and changes in bowel habits, yet the usual tests come back normal. This chapter explains why: IBS is a disorder of gut-brain interaction, a problem with how the gut and brain communicate, not with visible damage. Following Sam, you'll learn how doctors diagnose IBS from a pattern of symptoms using the Rome criteria (Rome IV, used in most research, and Rome V, the current version published in 2026), why alarm features always need checking, and why a "positive diagnosis" can replace years of testing. You'll also grade the evidence for the main treatments, including the low-FODMAP diet, cognitive behavioral therapy, gut-directed hypnotherapy, low-dose gut-brain neuromodulators, and peppermint oil, and learn why IBS trials show such a large placebo response.

Concepts Covered

1. Gut-Brain Interaction Disorder
2. Structural vs Functional Disease
3. Irritable Bowel Syndrome
4. Rome IV Criteria
5. IBS Subtypes
6. Functional Dyspepsia
7. Post-Infection IBS
8. Alarm Features
9. Positive Diagnosis Strategy
10. FODMAP
11. Low-FODMAP Diet
12. Cognitive Behavioral Therapy
13. Gut-Directed Hypnotherapy
14. Gut-Brain Neuromodulator
15. Peppermint Oil
16. Placebo Response

Prerequisites

- Chapter 2: The Vagus Highway (how signals travel between gut and brain)
- Chapter 7: Stress and the Gut (how stress changes gut movement and sensitivity)
- Chapter 8: Pain, Sensitivity, and the Gut (visceral hypersensitivity and central sensitization)
- Chapter 9: Inflammatory Bowel Disease (what structural gut inflammation looks like, for comparison)

When every test says normal



This is Sam's chapter, and it's about one of the most common gut conditions in the world. If you've ever been told "your tests are fine" while you still hurt, this chapter is for you. I carry a lot of the messages in this story, so it's a little personal for me too.

10.1 Sam's Year of "Normal"

The first time it happened, Sam was 14 and standing at the start line of a cross-country race. Cramps twisted low in his belly, and he barely made it to the porta-potty before the gun. He figured it was nerves. But it kept happening: before races, before big tests, and sometimes for no clear reason at all. Some weeks he had diarrhea, and other weeks he couldn't go for days. The pain usually eased after a bowel movement, and then it came back. (Sam is a fictional student who appears throughout this book.)

Over the next year, Sam had blood tests, stool tests, and a test for celiac disease. Everything came back "normal." Each time, he felt more confused, and a little embarrassed. A relative suggested it was "all in his head." His best friend Riya, who has Crohn's disease, told him to keep pushing for answers. Finally, at 15, a pediatric gastroenterologist sat down with him and said something he never forgot: "Your gut and brain aren't communicating well. That's real, it has a name, and we can treat it." The name was irritable bowel syndrome. This chapter explains what that doctor meant.

10.2 A Smoke Alarm Set Too Sensitive

Start with an everyday comparison. Imagine a smoke alarm in a kitchen. One kind of problem is a real fire: something is burning, and you can see the damage. A different kind of problem is an alarm set too sensitive. It goes off when you make toast. Nothing is burning, but the alarm is loud and the stress is real. You don't fix the oversensitive alarm with a fire extinguisher. You fix it by adjusting the alarm and the wiring that connects it to the control panel.

Crohn's disease and ulcerative colitis (Chapter 9) are like the real fire: there is inflammation and damage that tests can see. IBS is more like the oversensitive alarm. The gut tissue looks normal, but the signaling system that connects the gut, its nerves, and the brain is set differently, so normal amounts of gas, stretch, or movement can trigger pain and changes in bowel habits.

This idea has a name. A **gut-brain interaction disorder** is a condition in which gut symptoms come from problems in how the gut and brain communicate and process signals, such as increased gut sensitivity and altered gut movement, rather than from visible damage or inflammation. Doctors usually use the plural, "disorders of gut-brain interaction," shortened to DGBI. They are common: in the Rome Foundation Global Epidemiology Study of 73,076 adults in 33 countries (Sperber and colleagues, 2021), more than 40% of people who answered internet surveys met the criteria for at least one of these disorders.

These conditions used to be called "functional gastrointestinal disorders." That older word points to an important distinction. The idea of **structural vs functional disease** separates conditions in which tests show a physical abnormality, such as inflammation, ulcers, a tumor, or a blockage (structural disease), from conditions in which the organ looks normal on standard tests but doesn't work normally (functional disease). IBD is structural. IBS has been called functional.

The problem is that many people heard "functional" as "fake" or "imaginary." The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) now says that functional GI disorders are what doctors call disorders of gut-brain interactions, which are related to problems with how the brain and gut work together. And when the Rome Foundation released its newest criteria, Rome V, in 2026, it said it had minimized "functional" terminology in favor of more physiologically accurate language. Some names, like functional dyspepsia, keep the word for now.

Normal tests are not the same as nothing wrong



A colonoscopy can show ulcers, but it can't show how strongly a nerve fires or how loudly the brain "turns up" a gut signal. When tests that look for damage come back normal, that rules out damage. It doesn't rule out a real problem with signaling.

10.3 What Is Irritable Bowel Syndrome?

Irritable bowel syndrome (IBS) is a common disorder of gut-brain interaction marked by recurring belly pain linked to bowel movements and changes in how often stool happens or how it looks, without visible damage or disease in the digestive tract. NIDDK describes IBS as a group of symptoms that occur together, including repeated belly pain and changes in bowel movements, which may be diarrhea, constipation, or both. Other symptoms can include bloating, a feeling of not having finished a bowel movement, and whitish mucus in the stool.

NIDDK says IBS can be painful but doesn't lead to other health problems or damage the digestive tract. IBS does not turn into IBD, and it does not cause cancer. It does, however, affect daily life. The symptoms tend to come and go over years.

What goes wrong?

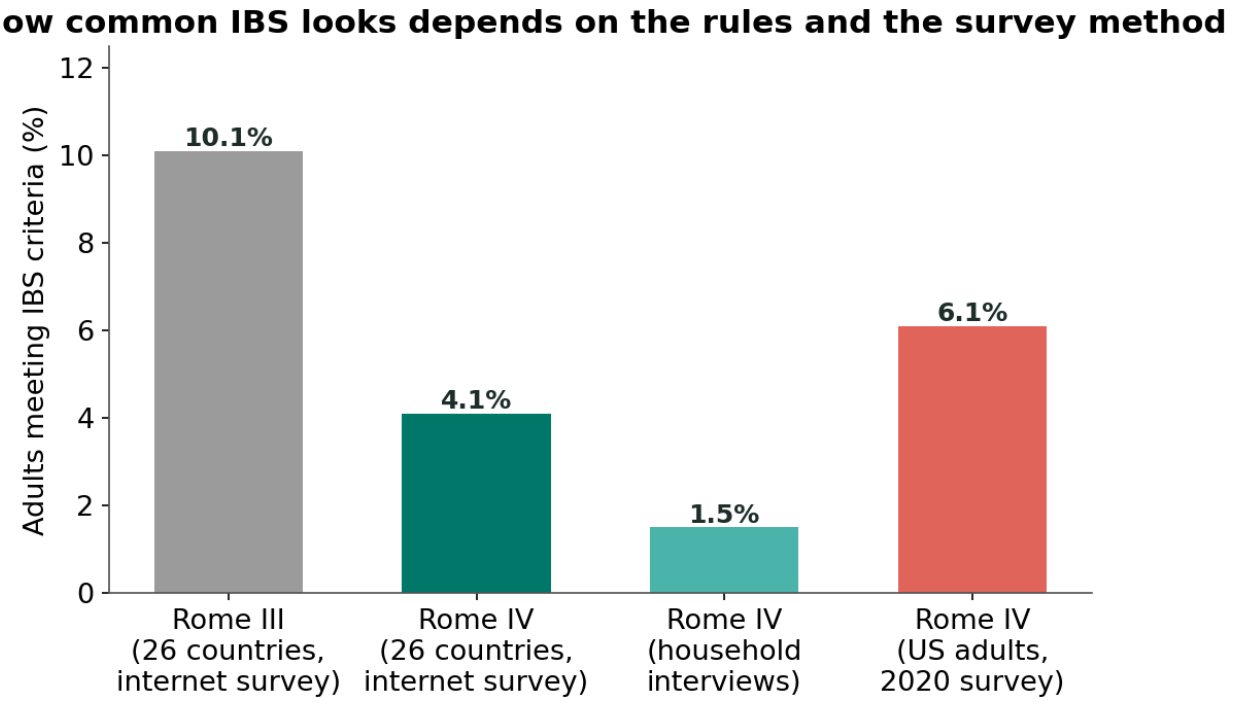
There's no single cause, and different factors matter for different people. A 2020 review in *The Lancet* by Black, Drossman, Talley, Ruddy, and Ford lists several mechanisms that seem to work together:

- **Two-way gut-brain dysregulation.** Signals between the gut and brain, through the vagus nerve, spinal nerves, and stress hormones (Chapters 2 and 7), are out of balance.
- **Visceral hypersensitivity.** The gut's sensory nerves, and the brain's processing of their signals, are turned up, so normal stretch feels painful (Chapter 8). NIDDK puts it simply: some people with IBS feel pain when a normal amount of gas or stool is in the gut.
- **Altered motility.** Food and stool may move too fast (leading to diarrhea) or too slowly (leading to constipation).
- **Microbiome and immune changes.** Studies find shifts in gut microbes and small changes in the gut's immune activity. These are mostly correlations, and their importance is still debated.

NIDDK lists factors that are more common in people with IBS and may play a role: stressful or difficult early life events, anxiety and depression, bacterial infections of the gut, food intolerances, and genes.

How common is IBS?

How many people have IBS depends on which criteria you use, so the numbers always need a label. By Rome IV criteria, 6.1% of US adults had IBS in a national online survey of 88,607 people done in May and June 2020 (Almario and colleagues, 2023). The authors noted that earlier US estimates were 4.7% to 5.3%, and they asked whether the COVID-19 pandemic, during which the survey ran, might have pushed the number up. Worldwide, by Rome IV criteria, about 4.1% of adults had IBS in internet surveys across 26 countries (Sperber and colleagues, 2021). In the same study, the older Rome III criteria gave 10.1%. The people were the same; only the rules changed. IBS is more common in women than in men.



Source: Sperber et al. 2021, Gastroenterology (Rome Foundation Global Epidemiology Study); Almario et al. 2023, Gastroenterology (US survey). Different rules and survey methods give very different numbers.

In the Almario survey, the most common subtype was IBS with mixed bowel habits (33.9% of people with IBS), the type Sam has. You'll learn what the subtypes mean in Section 10.4.

10.4 The Rome Criteria: Diagnosing From a Pattern

Because IBS doesn't leave visible damage, doctors diagnose it mainly from a pattern of symptoms. The standard rules come from the Rome Foundation, an international group of experts that has published criteria for disorders of gut-brain interaction since the 1990s. Each new edition updates the rules based on new evidence.

Rome IV: the version behind the research

The **Rome IV criteria** are the 2016 set of symptom-based diagnostic rules from the Rome Foundation for disorders of gut-brain interaction. For IBS in adults, they require:

1. **Recurrent belly pain, on average at least 1 day a week in the last 3 months,**
2. **linked to two or more of these three features:**
    - related to bowel movements (the pain changes with them),
    - a change in how often stool happens,
    - a change in how stool looks (its form),

3. **with the criteria met for the last 3 months, and symptoms that started at least 6 months before diagnosis.**

Most published IBS research, including the 6.1% US figure and the 4.1% worldwide figure, used Rome IV. That's why you'll keep seeing "by Rome IV criteria" in this book.

Kids and teens have their own version. For children and teens aged 4 to 18, the Rome IV IBS criteria require belly pain at least 4 days a month over at least 2 months, linked to one or more of the same three features, and symptoms that can't be fully explained by another medical condition after appropriate evaluation. In a child who also has constipation, the pain must not go away when the constipation is treated (if it does, the problem is constipation, not IBS).

Rome V (2026) keeps the 4 days a month, the 2 months, and the rule that another condition must not fully explain the symptoms, and adds that the pain comes and goes, is the main symptom, and doesn't happen only during menstrual periods. The Rome V pediatric paper also notes that a disorder of gut-brain interaction can exist alongside another condition that causes gut symptoms.

Rome V update (2026)

What changed. Rome V was published in the journal *Gastroenterology* in its May 2026 issue (see the Rome V bowel disorders paper and the overview of the Rome V process), and the Rome V book began shipping on June 1, 2026. It is now the current version. More than 140 experts from 27 countries worked on it. For adult IBS, Rome V requires **recurrent, but not continuous, abdominal pain or discomfort, on average at least 3 days a month in the last 3 months**, linked to two or more of the same three features, with the same timing rule (symptoms starting at least 6 months before diagnosis). As a supporting point, it adds that the pain or discomfort shouldn't be related only to menstrual periods. Rome V also separates strict research criteria from more flexible clinical criteria for everyday care, and minimizes the word "functional." **Why it matters.** "Discomfort" and "3 days a month" bring back ideas from the older Rome III, so more people with milder symptoms will qualify. In a 2026 UK survey of 1,275 adults with self-reported IBS (Staller and colleagues), 59.0% met Rome IV and 70.0% met Rome V, and people meeting Rome V had milder symptoms on average. Prevalence numbers based on Rome V will take years to build up, so for now, most numbers you read still come from Rome IV.

IBS subtypes

Not everyone with IBS has the same bowel habits, and the type matters because some medicines help one type and worsen another. **IBS subtypes** are categories of IBS based on a person's main stool pattern on days with abnormal bowel movements: IBS with constipation, IBS with diarrhea, IBS with mixed bowel habits, and IBS that doesn't fit any of these. Doctors judge stool form with the Bristol Stool Form Scale, a chart of seven stool types from hard lumps (types 1 and 2) to watery (types 6 and 7).

The table below summarizes the four subtypes, following the rules on the Rome Foundation's criteria page.

Subtype	Rule (on days with abnormal bowel movements)
IBS-C (constipation)	More than 25% hard or lumpy (types 1 to 2), fewer than 25% loose (types 6 to 7)
IBS-D (diarrhea)	More than 25% loose or watery, fewer than 25% hard or lumpy
IBS-M (mixed)	More than 25% hard or lumpy and more than 25% loose or watery
IBS-U (unclassified)	Meets IBS criteria but doesn't fit the other three patterns

Sam has IBS-M: some weeks are mostly diarrhea, others mostly constipation.

Pain is the anchor



Here's how I remember the IBS criteria: pain is the anchor, and it has to be linked to the bowel, through timing, frequency, or form. Bloating or diarrhea without that recurring, bowel-linked pain usually points to a different disorder of gut-brain interaction.

10.5 Other Disorders of Gut-Brain Interaction

IBS is the best known, but the Rome criteria describe dozens of disorders of gut-brain interaction, from the esophagus to the anus. Two more are worth knowing.

Functional dyspepsia

Functional dyspepsia is a disorder of gut-brain interaction of the upper gut, defined by bothersome fullness after meals, feeling full too early, or pain or burning in the upper belly (just below the breastbone), with no structural disease found to explain the symptoms, including on an upper endoscopy. That's the Rome IV wording; Rome V keeps the name and very similar criteria. Like IBS, the symptoms must have been present for the last 3 months, starting at least 6 months before diagnosis. People with functional dyspepsia often also have IBS, which makes sense if the underlying problem is how the gut and brain process signals, not damage in one spot.

Post-infection IBS

Sometimes IBS has a clear starting point. **Post-infection IBS** is IBS that develops after a bout of infectious gastroenteritis (a "stomach bug" or food poisoning caused by bacteria, viruses, or parasites), in a person who didn't have IBS before. A 2017 meta-analysis by Klem and colleagues combined 45 studies following 21,421 people after infectious enteritis. About 10.1% had IBS 12 months later, and the risk of IBS was about 4 times

higher in the year after an infection than in people who hadn't had one. Women, people with more severe infections, people who took antibiotics during the illness, and people with anxiety or depression were at higher risk.

These were observational studies, so they show strong links rather than proving every step of the mechanism. Still, post-infection IBS is some of the clearest human evidence that a physical event in the gut, not just stress, can start IBS. It is also a reminder that body and mind both shape who develops it.

10.6 Making the Diagnosis: Alarm Features and the Positive Diagnosis Strategy

How does a doctor know it's IBS and not something else, like IBD or celiac disease? For a long time, many doctors treated IBS as a "diagnosis of exclusion": rule out every other disease with test after test, and call whatever's left IBS. That's partly why Sam had a year of tests.

Alarm features

The first step is checking for warning signs. **Alarm features** are symptoms, signs, or history that suggest a disease other than IBS, such as inflammation, bleeding, or cancer, and that call for further medical evaluation. NIDDK lists symptoms that may point to a health problem other than IBS, and says doctors also ask about family history:

- anemia (too few red blood cells)
- bleeding from the rectum, or bloody or black, tarry stools
- unplanned weight loss
- a family history of celiac disease, colon cancer, or inflammatory bowel disease

When an alarm feature is present, doctors look further, often with blood tests, stool tests, or a colonoscopy, even if the symptoms otherwise fit IBS. Riya's story in Chapter 9 included weight loss and anemia, two alarm features that pointed toward Crohn's disease.

The positive diagnosis strategy

When there are no alarm features, the American College of Gastroenterology (ACG) suggests a different approach. A **positive diagnosis strategy** is an approach in which a clinician diagnoses IBS confidently from its typical symptom pattern (using the Rome criteria), a careful history and physical exam, the absence of alarm features, and a small number of targeted tests, instead of ordering every possible test to rule out all other diseases first. The ACG's 2021 IBS guideline, its first for IBS, suggests a positive diagnostic strategy over a strategy of exclusion, so that people can start the right treatment sooner. The same guideline suggests a blood test for celiac disease and a fecal calprotectin stool test (the inflammation "smoke detector" from Chapter 9) for people whose IBS symptoms include diarrhea, to rule out celiac disease and IBD.

So a positive diagnosis is not a guess. It is a confident diagnosis based on a recognizable pattern, plus a few smart checks. Think of how a doctor diagnoses a migraine: mostly from the pattern of the headaches, not from a brain scan for everyone.

A checklist can't diagnose you

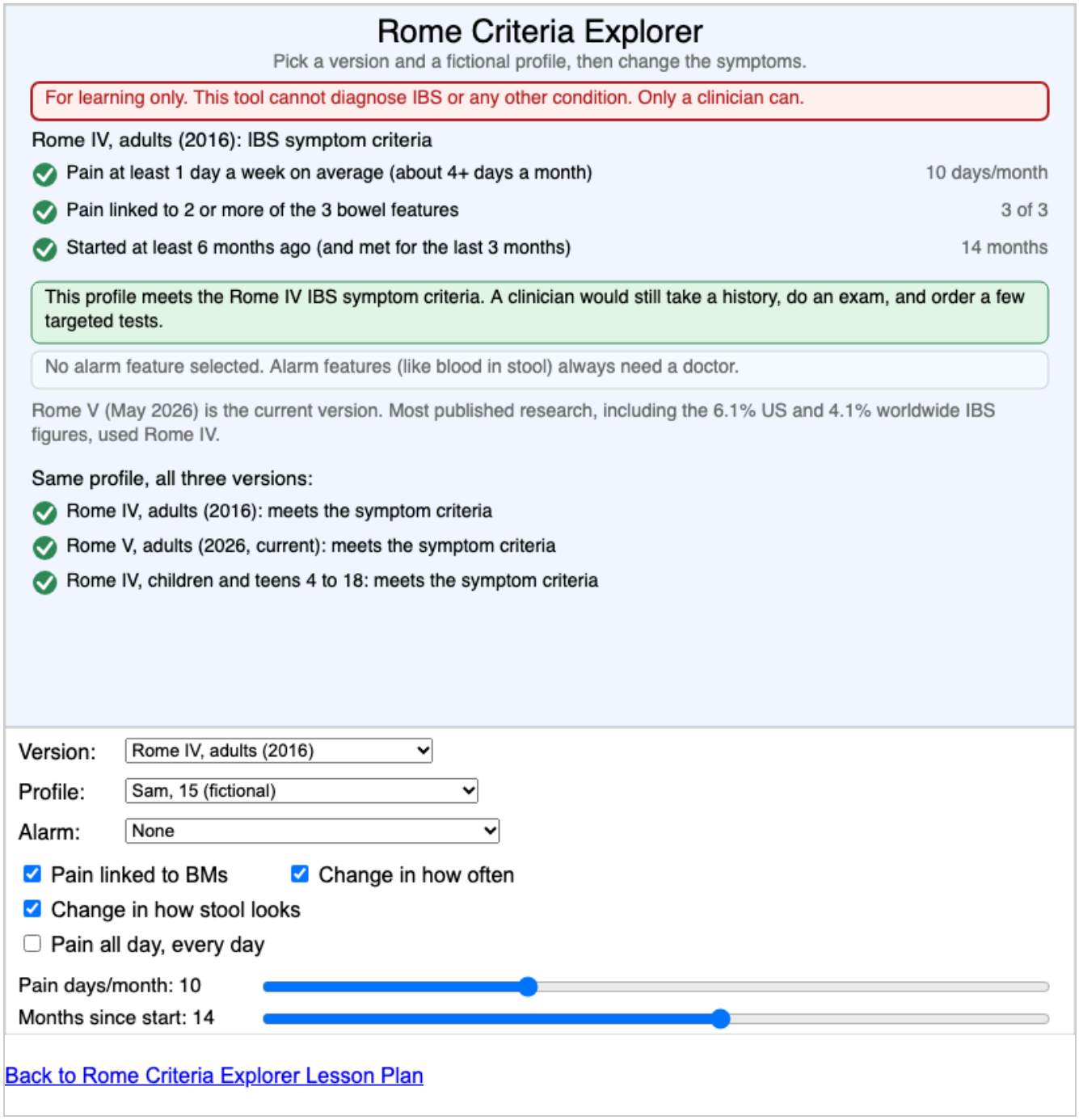


The Rome criteria look simple, so it's tempting to check the boxes and diagnose yourself or a friend. Please don't. Matching the pattern isn't enough without a clinician's history, exam, alarm-feature check, and the right tests, because conditions like IBD and celiac disease can look similar at first.

10.7 Try the Criteria: The Rome Criteria Explorer

The MicroSim below turns the Rome criteria into an interactive checklist. "Pain days per month" is how many days in a typical month the person has belly pain. "Months since start" is how long ago the symptoms began. The three checkboxes are the three bowel-related features, and the Alarm menu adds a warning sign. All the profiles are fictional, and the sim is for learning only: it cannot diagnose anyone.

Diagram: Rome Criteria Explorer



Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch10-rome-criteria-explorer/main.html

Open the Rome Criteria Explorer fullscreen

MicroSim specification: Rome Criteria Explorer

Type: microsim **sim-id:** ch10-rome-criteria-explorer
Library: p5.js
Status: Implemented
Bloom Level: Apply
Bloom Verb: apply, classify
Learning Objective: The learner will apply the symptom-based Rome criteria for IBS to fictional profiles, compare Rome IV (2016), Rome V (2026), and the Rome IV child and teen criteria, and recognize that alarm features require medical evaluation regardless of the checklist.

Canvas: 540 px drawing area plus 230 px controls (iframe 772 px); responsive to about 380 px wide.

Controls: Version select (Rome IV adults, Rome V adults, Rome IV children and teens 4 to 18); Profile select (Sam, Dana, Marcus, Leah, Omar, or Custom); Alarm select (none, blood in stool, unplanned weight loss, anemia, family history of colon cancer, IBD, or celiac disease); checkboxes for the three bowel features and for continuous pain; sliders for pain days per month (0 to 30) and months since start (0 to 24).

Rules: Rome IV adults: pain 4 or more days a month (simplified from at least 1 day a week), 2 or more features, onset 6 or more months ago. Rome V adults: pain or discomfort 3 or more days a month, not continuous, 2 or more features, onset 6 or more months ago. Child and teen: pain 4 or more days a month, 1 or more features, present 2 or more months. Any alarm feature shows a "needs medical evaluation" message.

Feedback: A permanent banner says the tool cannot diagnose. Each criterion shows a check or a cross, a result box names what is missing, and on wide screens a panel compares all three versions for the same profile.

Provenance: Rome Foundation Rome IV and Rome V criteria pages; NIDDK IBS diagnosis page (alarm features).

Start with Rome IV and the Sam profile: all three checks are green. Then choose **Dana**, who has pain only 3 days a month. She doesn't meet Rome IV, but switch the version to **Rome V** and she does. That one change, from "1 day a week" to "3 days a month," is a big reason Rome V will count more people as having IBS.

Next try **Marcus**, whose pain is there all day, every day. He meets Rome IV but not Rome V, because Rome V says IBS pain comes and goes; constant pain points toward a different disorder. Finally, try **Omar**. He meets the symptom criteria, but he has blood in his stool, an alarm feature. The checklist can't overrule a warning sign.

What this model leaves out

- Real diagnosis needs a clinician: a full history, a physical exam, a check for alarm features, and targeted tests. A checklist alone can never diagnose anyone.
- The sim simplifies "at least 1 day a week on average" to "4 or more days a month," and it assumes the symptoms were present for the last 3 months.
- It shows only a few alarm features; doctors consider others, along with age, medicines, and recent infections.
- It doesn't assign IBS subtypes (which need stool-form records) or include Rome V's new, more flexible clinical criteria.
- The child and teen version shown is Rome IV, and it skips two of its rules: another condition must not fully explain the symptoms, and in a child with constipation the pain must not go away when the constipation is treated. Rome V's pediatric criteria keep 4 days a month and 2 months, but add that the pain comes and goes, is the main symptom, and doesn't happen only during periods.

10.8 Treating IBS: Calming the Gut and the Gut-Brain Conversation

There's no single cure for IBS, but many treatments help, and the best plan usually combines several. NIDDK lists changes to what you eat and other lifestyle changes (such as physical activity, sleep, and reducing stress where possible), medicines, and mental health therapies. The British Society of Gastroenterology's 2021 guideline, built on careful analyses of trials, describes IBS as a disorder of gut-brain interaction and organizes treatment around that idea. Children and teens have their own guideline: a 2025 joint guideline from the European and North American pediatric gastroenterology societies reviewed 86 trials and noted major gaps in the evidence for young people. Most of the numbers below come from adult trials.

Here are the treatments in this chapter's concept list, with what the evidence shows. (As always, this is for learning. Treatment choices are for a person and their care team.)

The low-FODMAP diet

Some carbohydrates are hard for the small intestine to absorb. A **FODMAP** is a type of short-chain carbohydrate that is poorly absorbed in the small intestine and quickly fermented by gut bacteria; the name stands for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. When FODMAPs reach the colon, bacteria ferment them, making gas, and they also draw water into the bowel. In most people that causes little trouble. In a gut with turned-up sensitivity, the extra stretch can hurt. NIDDK lists foods containing FODMAPs, including some fruits (such as apples and pears), some vegetables (such as onions and garlic), milk products, wheat and rye products, honey, and sweeteners ending in "-ol," such as sorbitol.

The **low-FODMAP diet** is a structured, short-term eating plan, best done with a dietitian, in which a person first cuts back on high-FODMAP foods for a few weeks and then adds them back one group at a time to find which

ones trigger symptoms, so the long-term diet can be as broad as possible. NIDDK describes the same shape: try it for a few weeks, and if symptoms improve, slowly add FODMAP foods back.

The evidence is fairly good for the first phase. The ACG's 2021 guideline recommends a limited trial of a low-FODMAP diet to improve overall IBS symptoms. A 2022 network meta-analysis by Black, Staudacher, and Ford combined 13 randomized trials with 944 patients and ranked the low-FODMAP diet first among the diets studied for overall symptoms. But the authors noted that most trials were run in specialist clinics and didn't study the reintroduction and personalization phases, which are the parts meant for real life.

Hype Meter: "Low-FODMAP should be a forever diet"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. The low-FODMAP diet is designed as a short elimination phase followed by reintroduction, so that people end up avoiding only the foods that bother them. The trials that support it (13 trials, 944 patients in the 2022 meta-analysis) mostly tested short elimination periods, not lifelong restriction. Cutting out many foods for good can make eating stressful, make family meals and cultural foods harder, and limit the variety of foods (and fiber) that gut microbes use. **What would change the grade:** Long-term trials showing that permanent strict restriction works better and is safe compared with reintroduction and personalization. No such evidence exists.

Brain-gut behavioral therapies

Because IBS involves the gut-brain conversation, therapies that work on the brain's side of that conversation can help the gut. These are sometimes called brain-gut behavioral therapies. They are not a sign that the problem is "all in your head." They're a way to retune the alarm system.

Cognitive behavioral therapy (CBT) is a structured, skills-based form of talk therapy that helps people notice and change unhelpful thought patterns and behaviors, such as catastrophizing about symptoms or avoiding activities, which can reduce symptoms and their impact. In IBS, CBT often teaches people to break the loop in which worry about symptoms raises stress, stress raises gut sensitivity, and sensitivity raises symptoms and worry (Chapter 7).

Gut-directed hypnotherapy is a type of hypnotherapy in which a trained therapist guides a person into a deeply relaxed, focused state and uses suggestions and imagery aimed at calming the gut and changing how gut sensations are processed. It isn't stage hypnosis, and the person stays in control. Courses usually involve several sessions.

How well do these therapies work? A 2020 network meta-analysis by Black and colleagues combined 41 randomized trials with 4,072 adults. CBT (both self-guided and face-to-face) and gut-directed hypnotherapy had the largest evidence base and helped more people improve than control treatments. A 2024 analysis of 42 trials and 5,220 participants (Goodoory and colleagues) found that several brain-gut behavioral therapies also improved belly pain specifically, with none clearly better than the others. Both teams warned that many trials

had a high risk of bias, so the benefits may be overestimated. For children and teens, the 2025 ESPGHAN/NASPGHAN guideline recommends hypnotherapy (based on moderate-certainty evidence) and CBT (based on low-certainty evidence) as treatment options.

Hype Meter: "Gut-directed hypnotherapy helps IBS"

Strong	**Moderate**	Preliminary	Hype

Verdict: Moderate. In a 2020 network meta-analysis of 41 randomized trials (4,072 adults), gut-directed hypnotherapy was one of the therapies with the best evidence for improving IBS symptoms, along with CBT, and a 2024 analysis of 42 trials found it also helped belly pain. These are real human trials. But many had a high risk of bias, it's hard to "blind" people to whether they're getting hypnotherapy, and the authors said the benefits may be overestimated. The ACG suggests gut-directed psychotherapy for IBS.
What would change the grade: Larger, well-designed trials with strong control conditions and long follow-up, including in teens, could move it up to Strong. Trials showing the benefit disappears against a good placebo-like control would move it down.

Gut-brain neuromodulators

Some medicines act on the nerves and brain circuits that process gut signals. A **gut-brain neuromodulator** is a medicine that acts on the nervous system's processing of gut signals, often a low dose of a medicine first developed as an antidepressant, used to reduce gut pain and change gut movement in disorders of gut-brain interaction. The best studied are tricyclic antidepressants (TCAs). This confuses a lot of people. In IBS, TCAs are used at low doses as gut-brain neuromodulators, not to treat depression. A doctor prescribing one isn't saying the person is depressed. The medicine is turning down pain signaling.

A 2026 network meta-analysis by Khasawneh and colleagues combined 68 randomized trials with 6,694 adults. Another class of medicines called SNRIs ranked first, but based on only six small trials; TCAs ranked second, based on 15 trials with 1,519 people. The authors rated the overall certainty of the evidence as low or very low for most comparisons. Guidelines differ in how strongly they back TCAs. The ACG's 2021 guideline gives them a strong recommendation for overall IBS symptoms, while the American Gastroenterological Association's 2022 guideline for IBS with diarrhea includes TCAs among several options, with a conditional recommendation.

Peppermint oil

Peppermint oil is an oil from the peppermint plant, usually taken in coated capsules that release it in the intestine, that relaxes gut smooth muscle and is used to ease IBS symptoms such as pain and cramping. It works somewhat like the antispasmodic medicines that relax gut muscle. A 2022 meta-analysis by Ingrosso and colleagues combined 10 randomized trials with 1,030 patients. Peppermint oil did better than placebo for overall symptoms and belly pain, but side effects were more common than with placebo, and the authors rated the quality of the evidence as very low.

On this book's scale, that makes it Preliminary: it may help some people, but the trials behind it are low quality, so the size of the benefit is uncertain. Being sold at a drugstore doesn't make a product right for everyone, so it's still a good idea to ask a doctor first.

The table below compares the treatments we just covered.

Treatment	What it targets	Evidence highlight	Our read
Low-FODMAP diet (with reintroduction)	Gas and stretch from fermented carbohydrates	13 trials, 944 patients; ranked first among diets	Good for short-term relief; reintroduction understudied
Cognitive behavioral therapy	Thought and behavior loops that amplify symptoms	Among the best-studied therapies (41 trials total)	Moderate; trials at risk of bias
Gut-directed hypnotherapy	Gut sensations and how the brain processes them	Among the best-studied therapies	Moderate
Low-dose TCAs (neuromodulators)	Pain signaling in nerves and brain	Ranked second in a 68-trial analysis (15 TCA trials)	Moderate; low certainty
Peppermint oil	Gut smooth muscle spasm	10 trials, 1,030 patients	Preliminary; very low quality, more side effects

10.9 The Placebo Response: Why IBS Trials Are Tricky

Every IBS treatment claim runs into the same problem. In drug trials, a lot of people who get the fake pill feel better too.

The **placebo response** is the improvement in symptoms that people experience after receiving an inactive treatment (a placebo), caused by things like expectations, attention and care, the natural ups and downs of symptoms, and changes in how the brain processes body signals. It doesn't mean the person "was faking." Expectations and attention can really change pain processing, the same brain systems that IBS involves. Part of the response also comes from symptoms naturally swinging back toward average over time.

How big is it in IBS? A 2021 meta-analysis by Bosman and colleagues looked at 73 randomized drug trials in adults with IBS. Among people given placebo, 27.3% reported overall improvement, and 34.4% reported improvement in belly pain. That's why a new treatment must beat placebo in a controlled trial, not just help "a

lot of people." If a supplement ad says "70% of users felt better," your next question should be: compared with what?

One unusual study pushed the idea further.

How to read a gut-brain claim: the 2010 open-label placebo trial in IBS

Question	This study
Mouse or human?	Human. 80 adults with IBS (70% women, average age 47) at one academic center in Boston.
Correlation or cause?	Tests cause, partly. People were randomly assigned to open-label placebo pills (they were told the pills were inactive) or to no treatment, with the same amount of attention from the staff. Neither group was blinded, which a pill-versus-no-pill design can't do.
How many?	Small: 37 in the placebo group and 43 in the no-treatment group. Some outcome data were missing at the end (about 13%).
How long?	Short: 3 weeks.
Who paid for it?	Mostly grants from the US National Center for Complementary and Alternative Medicine (part of NIH), plus a gift from the Bernard Osher Foundation. One author had consulted for drug companies that had no relationship to the study.
Is something being sold?	No product. The placebo pills weren't for sale.

In this trial by Kaptchuk and colleagues, published in 2010, people were told honestly that the pills were "like sugar pills" and were given a hopeful explanation of how placebos can work. At 3 weeks, 59% in the placebo group reported adequate relief of their IBS symptoms, compared with 35% in the no-treatment group. The open-label placebo group also scored better on global improvement and symptom severity.

What should you conclude? It's a small, short, single-center study without blinding, so it's a reason for curiosity, not a new treatment. But it shows something important about IBS: how symptoms are explained and how care is delivered can change how people feel. That's consistent with a gut-brain disorder, and it's exactly why treatment claims need placebo-controlled trials.

10.10 Is IBS "Just Anxiety"?

Sam has test anxiety, and his IBS flares before tests and races. So is his IBS just anxiety in disguise? A lot of people believe this, and hearing it can make patients feel dismissed.

Hype Meter: "IBS is just anxiety"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. Anxiety and depression are more common in people with IBS: a 2019 meta-analysis of 73 studies (Zamani and colleagues) found anxiety symptoms in 39.1% and depression symptoms in 28.8%. A diagnosed anxiety disorder was present in about 23%, so most people with IBS don't have one. Stress can worsen gut symptoms (Chapter 7), but IBS also involves measurable changes in gut sensitivity and movement, and it can start after a gut infection. The 2020 *Lancet* review notes that it isn't clear whether psychological symptoms come before IBS or are driven by it. A brain-gut therapy helping IBS doesn't prove IBS is "psychological"; it shows the gut-brain link is two-way. **What would change the grade:** Nothing likely. The evidence points to a two-way gut-brain disorder, not to anxiety alone.

The careful version is this: the brain and gut influence each other in both directions. Worry can turn up gut sensitivity and change motility, and months of unpredictable pain and urgent bathroom trips can cause worry. Treating both sides, the gut and the brain, often works better than treating either alone. Chapter 11 explores these two-way links in more depth.

Words also matter. Many people with IBS have been told "it's just stress" or "nothing's wrong," and the 2020 *Lancet* review notes that patients with these disorders can feel stigmatized, and that the diagnosis often isn't explained well. Hearing a clear explanation, like the one Sam's doctor gave, is part of good care.

If you're going through this

If you have IBS, your pain is real, even if every test was normal. A normal colonoscopy rules out damage, not suffering. It can help to keep a simple symptom diary for your care team, to ask your school counselor or nurse about a plan for restroom access during tests, and to ask your doctor about gut-brain therapies like CBT or gut-directed hypnotherapy. Be wary of posts selling "cures," and talk to your doctor before starting any supplement or strict diet.

For families

The most helpful thing you can say to someone with IBS is that you believe them. Phrases like "it's all in your head" or "just relax" can make them feel dismissed and can even add to the stress that worsens symptoms. Helpful support looks like flexibility around plans, not commenting on bathroom trips, and including foods they can eat at family meals. If a dietitian recommends a low-FODMAP trial, remember that it's meant to be temporary, with foods added back, so family dishes can usually return.

At the Bedside: Sam's Story, Naming the Problem

Meet the patient (fictional)

Sam is 15, a high school sophomore and cross-country runner. For more than a year he has had cramping lower belly pain about two or three days a week, which usually eases after a bowel movement. Some weeks his stools are loose and urgent, and other weeks they're hard and infrequent. Symptoms are worst before big tests and races. His parents notice he skips breakfast on race days and seems more anxious at school.

What the doctor checks: The pediatric gastroenterologist takes a careful history: how often the pain happens, how it relates to bowel movements, stool patterns, sleep, school, stress, recent infections, and family history. She asks specifically about alarm features: blood in the stool, weight loss, and family members with IBD, celiac disease, or colon cancer. She checks his growth chart and examines his belly. His earlier blood tests (including a blood count and a celiac test) and his fecal calprotectin were normal.

Connecting the signals: Sam's pain is recurrent, linked to bowel movements, and comes with changes in how often stool happens and how it looks. It has lasted well over 6 months. That fits the Rome IV criteria for children and teens, and the adult version too. He has no alarm features, a normal calprotectin argues against IBD, and a normal celiac test argues against celiac disease. Symptoms that flare with stress fit the gut-brain loop from Chapter 7.

Diagnosis: Irritable bowel syndrome with mixed bowel habits (IBS-M), made with a positive diagnosis strategy.

Why it happens: Sam's gut-brain signaling is set too sensitive. His gut nerves and brain amplify normal stretch into pain (visceral hypersensitivity), and his gut movement speeds up or slows down, especially when stress hormones and nerve signals surge before tests and races. Stress didn't create his IBS out of nothing, but it turns the volume up.

The mind-body side: Sam had started to feel that his body couldn't be trusted, and his test anxiety and gut symptoms fed each other. His doctor explained the diagnosis clearly and said it was real, which Sam said was a relief in itself. She referred him to a psychologist who uses cognitive behavioral therapy for test anxiety and gut symptoms, and to a program of gut-directed hypnotherapy recordings, which is where he learned the gut-directed relaxation he practices before races. His school set up a plan allowing restroom breaks during exams.

Treatment today: Along with CBT and gut-directed hypnotherapy, Sam is working with a dietitian on a short low-FODMAP trial with planned reintroduction, so he can learn which foods, if any, are triggers without giving up the foods he loves. His doctor talked with him about other options, such as medicines, if symptoms stay bothersome. When his cousin keeps posting about a "gut-healing" supplement, Sam asks his care team before trying anything, and checks whether the claims come from placebo-controlled trials.

What's new in research: In May 2026 the Rome Foundation published Rome V, which brings back "discomfort," lowers the pain frequency to at least 3 days a month, and excludes continuous pain. A 2026 UK survey of 1,275 adults with self-reported IBS found that 70.0% met Rome V compared with 59.0% for Rome IV, and that

people meeting Rome V had milder symptoms on average (Staller et al., *Clinical Gastroenterology and Hepatology*, 2026). **Evidence grade: Moderate.** The criteria themselves are official, but studies on how Rome V changes diagnosis and research are only beginning.

Your turn: reason through a variation

Suppose Sam's teammate Jordan, 17, has the same kind of belly pain and diarrhea, but over the last two months he has also lost weight without trying and has seen blood in his stool. His older brother has Crohn's disease. Jordan says, "I meet the Rome criteria, so it's IBS like Sam's." What's wrong with that reasoning?

Answer: Jordan has three alarm features: unplanned weight loss, blood in the stool, and a family history of IBD. Alarm features mean he needs a medical evaluation, which might include blood tests, a fecal calprotectin test, and a colonoscopy, because his symptoms could come from IBD or another structural disease. Also, his symptoms have lasted only two months, so as a teen he would barely meet the child and teen criteria, and as an adult he wouldn't meet the 6-month rule. Matching part of a checklist never overrules a warning sign.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: "Functional" means the symptoms are fake or imaginary.
Reality: "Functional" meant the gut looks normal on tests but doesn't work normally. IBS involves real changes in gut sensitivity, movement, and gut-brain signaling. That's why the field now prefers "disorders of gut-brain interaction," and Rome V (2026) minimizes the word "functional."

Myth: IBS damages the bowel or leads to cancer.
Reality: NIDDK says IBS can be painful but doesn't lead to other health problems or damage the digestive tract. It does not turn into IBD or cancer, though new alarm features should always be checked by a doctor.

Myth: IBS can be diagnosed only after every other disease has been ruled out with tests.
Reality: The ACG's 2021 guideline suggests a positive diagnosis strategy: a typical symptom pattern, no alarm features, and a few targeted tests (such as a celiac blood test and fecal calprotectin when diarrhea is present). This lets people start treatment sooner.

Myth: Everyone with IBS should go gluten-free.
Reality: Some people with IBS feel better avoiding certain foods, but the best-studied diet approach is a short low-FODMAP trial with reintroduction, guided by a dietitian, to find individual triggers. NIDDK notes that doctors don't recommend starting a gluten-free diet before celiac testing, because it can affect the results, so diet changes should be discussed with a doctor or dietitian first.

Myth: If a doctor prescribes an antidepressant for IBS, it means the IBS is really depression.
Reality: Low doses of tricyclic antidepressants are used as gut-brain neuromodulators that turn down pain signaling, not to treat depression.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Doctors can't fix IBS because it's all in your head. My 3-step mindset reset cured mine in a week. Sign up below!"

Grade: Hype. IBS isn't "all in your head": it involves measurable changes in gut sensitivity and movement and can start after a gut infection. Brain-gut therapies such as CBT and gut-directed hypnotherapy do have real trial evidence, but they take weeks of structured sessions, the trials have risk-of-bias problems, and none promises a cure in a week. One person's story can't separate the program from natural ups and downs or the placebo response, and a sign-up link means something is being sold. A careful version: "Gut-brain therapies like CBT and gut-directed hypnotherapy can reduce IBS symptoms for many people, alongside other treatments."

2. Predict: Sam has a big chemistry final on Friday and a regional race on Saturday. Using the gut-brain loop, predict what might happen to his symptoms that week, and what tools from his care plan could help.

Stress before the final and the race can activate the HPA axis and the sympathetic nervous system (Chapter 7), which can change gut movement and turn up gut sensitivity, so Sam may have more cramping and urgency. Worry about symptoms during the test could add to the loop. His gut-directed relaxation, CBT skills for test anxiety, his school's restroom plan, and familiar foods he knows don't trigger symptoms could all help.

3. Explain: Sam's friend asks, "If your colonoscopy and blood tests were normal, how can your doctor be sure it's IBS?" Explain how a positive diagnosis works.

IBS is diagnosed from its typical pattern: recurrent pain linked to bowel movements and to changes in stool frequency or form, lasting long enough to meet the Rome criteria. The doctor also takes a careful history, examines the patient, checks for alarm features such as bleeding or weight loss, and orders a few targeted tests, such as a celiac test and fecal calprotectin. When the pattern fits and there are no alarm features, the diagnosis is made with confidence, not by elimination.

4. Apply: A 22-year-old has had belly pain about 3 days a month for a year. It's linked to bowel movements and to looser stools, comes and goes, and she has no alarm features. Does she meet Rome IV? Rome V?

She doesn't meet Rome IV, which requires pain on average at least 1 day a week (about 4 or more days a month). She does meet Rome V's symptom criteria: recurrent, not continuous pain at least 3 days a month, linked to two of the three features, starting at least 6 months ago. This shows why Rome V will classify more people, often with milder symptoms, as having IBS. Only a clinician could actually diagnose her.

5. Read the data. In 2026, Staller and colleagues surveyed 1,275 adults in the United Kingdom who said they had IBS, and checked which versions of the Rome criteria each person met:

Criteria version	People meeting the IBS criteria	Percent
Rome III (older version)	995	78.0%
Rome IV (2016)	752	59.0%
Rome V (2026)	893	70.0%

5. What does this data show, and what can't it show?

It shows that the version of the criteria changes who counts as having IBS: among the same 1,275 people, Rome IV was the strictest, and Rome V included about 11 percentage points more people than Rome IV. That's why prevalence figures must name their criteria. It can't show how many people in the general population have IBS, because everyone surveyed already said they had IBS, and it can't show which version is "correct" or better for patients. A helpful follow-up would apply all three versions to a large, random sample of the general population and follow people over time to see which criteria best predict symptoms and response to treatment.

Exercises

Remember

1. List the three bowel-related features in the Rome criteria for IBS.

Answer

Pain related to bowel movements (defecation), a change in how often stool happens (frequency), and a change in how stool looks (form or appearance).

1. Name four alarm features that call for further medical evaluation in someone with IBS-like symptoms.

Answer

Any four of: anemia, rectal bleeding or bloody or black stools, unplanned weight loss, and a family history of celiac disease, colon cancer, or inflammatory bowel disease.

Understand

1. Explain the difference between structural and functional disease, using IBD and IBS as examples, and explain why the field is moving away from the word "functional."

Answer

Structural disease shows a physical abnormality on tests, like the ulcers and inflammation of IBD. Functional disease means the organ looks normal but doesn't work normally, as in IBS. The word "functional" was often misheard as "fake," so experts now prefer "disorders of gut-brain interaction," and Rome V minimizes the word.

1. Explain why the low-FODMAP diet is meant to be temporary, and what the reintroduction phase is for.

Answer

The elimination phase is a short test to see whether FODMAPs drive symptoms. Reintroduction adds FODMAP groups back one at a time to find a person's specific triggers, so they can eat as broad and varied a diet as possible over the long term. Long-term strict restriction isn't supported by evidence and can make eating harder.

Apply

1. Use the Rome Criteria Explorer. For each of the three versions, find the smallest number of pain days per month that meets the criteria for the Sam profile. Make a table and explain why the numbers differ.
2. A friend says, "My stomach hurts before every test, so I have IBS." Using the Rome criteria and alarm features, write three questions a doctor might ask before reaching any conclusion.

Analyze

1. The US prevalence of IBS was 6.1% by Rome IV in one study, while an older figure on the NIDDK website says about 12%. Analyze at least two reasons these numbers could differ so much.
2. In the Kaptchuk 2010 trial, 59% of the open-label placebo group reported adequate relief, compared with 35% of the no-treatment group. Analyze which parts of this result could come from expectations, attention, natural symptom changes, and the lack of blinding.

Evaluate

1. Evaluate this headline: "Hypnosis cures IBS, scientists say." Use the evidence from this chapter to grade it and rewrite it accurately in 15 words or fewer.
2. Some experts think Rome V's lower pain threshold will help more people get diagnosed and treated; others worry it will label people with mild symptoms. Evaluate both sides using the Staller 2026 data, and state which concern you find more convincing.

Create

1. Design a one-page guide for a high school nurse's office explaining IBS to students. Include what IBS is, why normal tests don't mean "nothing is wrong," the alarm features that mean "see a doctor," and two evidence-based treatment approaches, without giving medical advice.
2. Design a randomized trial to test whether an app-based gut-directed hypnotherapy program reduces IBS pain in teens. Describe the control group (and how you'd handle the placebo response), how many participants you'd want, what you'd measure, and how long you'd follow them.

Key Takeaways

- IBS is a disorder of gut-brain interaction: real, recurring pain and bowel changes caused by altered gut sensitivity, gut movement, and gut-brain signaling, not by visible damage. It doesn't damage the bowel or cause cancer.
- "Structural vs functional" separates diseases with visible damage (like IBD) from those where the organ looks normal but works differently. "Functional" never meant fake, and Rome V (2026) minimizes the word.
- Rome IV (2016) is the version behind most research: pain at least 1 day a week, linked to 2 of 3 bowel features, starting at least 6 months ago. By Rome IV criteria, about 6.1% of US adults and 4.1% of adults worldwide (internet surveys) have IBS. Rome V is now current and counts pain or discomfort at least 3 days a month, if it isn't continuous.
- IBS subtypes (C, D, M, U) depend on stool form. Functional dyspepsia and post-infection IBS are related disorders; about 10% of people develop IBS in the year after a gut infection.
- Alarm features (bleeding, weight loss, anemia, certain family history) always need evaluation; without them, a positive diagnosis strategy with a few targeted tests replaces years of testing.
- Treatments with trial evidence include a short low-FODMAP diet with reintroduction, CBT, gut-directed hypnotherapy, low-dose gut-brain neuromodulators, and peppermint oil, each with limits on the evidence.
- IBS trials show a large placebo response (about 27% overall improvement on placebo), so every treatment claim needs a placebo-controlled trial.

You can explain the 'invisible' gut disorder!



You now know why normal tests don't mean nothing's wrong, how the Rome criteria work, and how to judge IBS treatment claims. Next, in Chapter 11, we'll follow the two-way street between the gut, anxiety, and depression, and see why "which came first?" is such a hard question.

Quiz: IBS and Disorders of Gut-Brain Interaction

Test your understanding of Chapter 10. Choose the best answer, then click **Show Answer** to check.

Question 1

Under the Rome IV criteria for adults, how often must IBS belly pain occur?

A. Every day, all day, for at least 1 year

B. At least 3 days a month, if it is not continuous

C. On average at least 1 day a week in the last 3 months

D. Only once, if it was severe

Show Answer

The correct answer is **C**. Rome IV requires recurrent belly pain on average at least 1 day a week in the last 3 months, linked to two or more of the three bowel features, with symptoms starting at least 6 months before diagnosis. Option B describes Rome V (2026), the newer and now current version.

Concept Tested: Rome IV Criteria **Bloom's Level:** Remember

Question 2

What does the acronym FODMAP refer to?

A. Short-chain carbohydrates that are poorly absorbed and quickly fermented by gut bacteria

B. A group of proteins in wheat that trigger celiac disease

C. Fats that slow down digestion in the stomach

D. Chemicals made by the brain that control gut movement

Show Answer

The correct answer is **A**. FODMAP stands for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols: carbohydrates that are poorly absorbed in the small intestine and fermented by bacteria in the colon, producing gas and drawing in water. Option B describes gluten, which is a protein, not a FODMAP.

Concept Tested: FODMAP **Bloom's Level:** Remember

Question 3

Which of the following is an alarm feature that calls for further medical evaluation in someone with IBS-like symptoms?

A. Pain that improves after a bowel movement

B. Bloating after meals

C. Symptoms that get worse before exams

D. Blood in the stool

Show Answer

The correct answer is **D**. Rectal bleeding or bloody stools can signal a structural disease such as IBD and always need evaluation. Option A is actually one of the typical IBS features in the Rome criteria, not a warning sign.

Concept Tested: Alarm Features **Bloom's Level:** Remember

Question 4

Why do experts now prefer the term "disorders of gut-brain interaction" over "functional gastrointestinal disorders"?

A. Because new tests can now see damage in the gut in every case of IBS

B. Because "functional" was often misheard as "fake," while the new term describes the real problem in gut-brain signaling

C. Because IBS has been shown to be a form of inflammatory bowel disease

D. Because the condition is caused only by anxiety

Show Answer

The correct answer is **B**. "Functional" meant the gut looks normal but works differently, yet many people heard it as "imaginary." The new term names the actual problem: how the gut and brain communicate and process signals. Rome V (2026) minimizes the word "functional." Option C is wrong because IBS is not a form of IBD.

Concept Tested: Structural vs Functional Disease **Bloom's Level:** Understand

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Question 5

What is the purpose of the reintroduction phase of the low-FODMAP diet?

A. To find which specific FODMAP groups trigger a person's symptoms so their long-term diet can be as broad as possible

B. To prove that the person has celiac disease

C. To replace the elimination phase, which is optional

D. To permanently remove all FODMAP foods from the diet

Show Answer

The correct answer is **A**. The diet is a short elimination followed by adding food groups back one at a time, so people end up avoiding only true triggers. Option D describes the "forever diet" idea, which this chapter grades as Hype.

Concept Tested: Low-FODMAP Diet **Bloom's Level:** Understand

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Question 6

A doctor prescribes a low dose of a tricyclic antidepressant for a teen with IBS. What is the best explanation?

A. The doctor has decided the teen's IBS is really depression

B. The medicine kills harmful gut bacteria

C. At low doses, the medicine acts as a gut-brain neuromodulator that can turn down pain signaling

D. The medicine is a type of FODMAP

Show Answer

The correct answer is **C**. In IBS, low-dose tricyclic antidepressants are used as gut-brain neuromodulators to reduce pain and change gut movement, not to treat depression. Option A is the common misunderstanding this chapter corrects.

Concept Tested: Gut-Brain Neuromodulator **Bloom's Level:** Understand

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Question 7

Kai, 20, got food poisoning from a bacterial infection last spring. Since then he has had recurring belly pain linked to bowel movements and loose stools, and his tests show no inflammation. Which concept best fits his situation?

A. Functional dyspepsia

B. Ulcerative colitis

C. Hirschsprung disease

D. Post-infection IBS

Show Answer

The correct answer is **D**. IBS that starts after a bout of infectious gastroenteritis is called post-infection IBS. A 2017 meta-analysis found that about 10% of people had IBS 12 months after infectious enteritis. Ulcerative colitis (option B) would show inflammation on tests, and functional dyspepsia (option A) involves upper-belly symptoms like early fullness.

Concept Tested: Post-Infection IBS **Bloom's Level:** Apply

Question 8

A 30-year-old has had recurring belly pain about 2 days a week for a year. The pain eases after bowel movements and comes with harder, less frequent stools. She has no alarm features, and a doctor confirms the pattern with a careful history and exam. Which approach does the ACG's 2021 guideline suggest?

A. Order every available test to rule out all other diseases before considering IBS

B. Make a positive diagnosis of IBS based on the symptom pattern, history, exam, and the absence of alarm features

C. Tell her the symptoms are caused by stress and need no treatment

D. Recommend a lifelong gluten-free diet

Show Answer

The correct answer is **B**. The ACG suggests a positive diagnostic strategy over a strategy of exclusion so people can start treatment sooner. Option A describes the older "diagnosis of exclusion" approach, which can mean years of unnecessary tests, as Sam experienced.

Concept Tested: Positive Diagnosis Strategy **Bloom's Level:** Apply

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Question 9

In a 2021 meta-analysis of 73 IBS drug trials, 27.3% of people given placebo reported overall improvement. What is the most important lesson for judging an IBS treatment claim?

A. Placebos cure IBS, so medicines are unnecessary

B. People in IBS trials usually lie about their symptoms

C. A treatment that helps 27% of people must be effective

D. A treatment must do better than placebo in a controlled trial, because many people improve without an active treatment

Show Answer

The correct answer is **D**. Expectations, attention, and natural ups and downs mean many people feel better on placebo, so only a comparison with placebo shows whether a treatment adds a real benefit. Option C ignores this baseline, and option B misunderstands the placebo response, which involves real changes in how symptoms are experienced.

Concept Tested: Placebo Response **Bloom's Level:** Analyze

Question 10

In a 2026 survey of 1,275 UK adults with self-reported IBS, 59.0% met Rome IV and 70.0% met Rome V. What is the best conclusion?

A. The criteria version changes who counts as having IBS, so prevalence numbers must say which version they used

B. IBS became more common between 2016 and 2026

C. Rome V is more accurate than Rome IV

D. About 70% of UK adults have IBS

Show Answer

The correct answer is **A**. The same people were classified differently depending on the rules, which is why this book always writes "by Rome IV criteria" next to research numbers. The survey included only people who already said they had IBS, so option D is wrong, and it can't show which version is more accurate (option C).

Concept Tested: Rome IV Criteria **Bloom's Level:** Analyze

Chapter 11: Anxiety, Depression, and the Gut

Summary

People with gut conditions such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) report anxiety and depression symptoms much more often than other people. This chapter asks the obvious next question: which comes first? You will learn what anxiety disorders, depression, and gut-specific anxiety are, how researchers measure them, and why a link between two things can come from either direction or from a hidden third factor. You will see real evidence that the gut-brain street runs both ways, weigh the ideas that inflammation and gut microbes play a role, and learn why mental-health care belongs inside gut care, along with how and where to get help.

Concepts Covered

1. Anxiety Disorder
2. Major Depressive Disorder
3. GI-Specific Anxiety
4. Psychiatric Comorbidity
5. Bidirectional Relationship
6. Meta-Analysis
7. Symptom Questionnaire
8. Cohort Study
9. Reverse Causation
10. Confounding Variable
11. Inflammatory Depression Theory
12. Illness Burden
13. Microbiota Transfer Study
14. Help-Seeking
15. Crisis Resources
16. Integrated Care

Prerequisites

- Chapter 3: Meet the Microbiome (correlation vs causation, germ-free mice)
- Chapter 4: The Immune System as a Sense Organ (cytokines and sickness behavior)
- Chapter 7: Stress and the Gut (the HPA axis and stress)
- Chapter 8: Pain, Sensitivity, and the Gut (visceral hypersensitivity)
- Chapter 9: Inflammatory Bowel Disease (Crohn's disease, ulcerative colitis, flares, remission)
- Chapter 10: IBS and Disorders of Gut-Brain Interaction (irritable bowel syndrome)

When the gut and mood travel together



If you live with a gut condition, you may have noticed that worry and low mood often show up alongside your symptoms. This chapter takes that experience seriously and asks a scientist's question about it: which way do the arrows point? Along the way, you'll pick up tools for reading health research that work far beyond the gut.

11.1 Which Came First?

Riya has noticed a pattern. In the days before a Crohn's flare, she often feels tense and on edge, the kind of anxious that makes it hard to focus on her violin part in orchestra. Then the belly pain and diarrhea arrive. Afterward she wonders: did the worry trigger the flare? Or was the flare already starting, quietly, and her body felt it before she did? (Riya is a fictional student who appears throughout this book.)

Her best friend Sam has his own version. His IBS gets worse before big tests, and he has test anxiety. On a bad morning, it's hard to tell whether his nervous stomach is making him anxious or his anxiety is making his stomach nervous.

They are not alone. A 2021 analysis of 77 studies found that about one in three adults with IBD screened positive for anxiety symptoms, and about one in four for depression symptoms. Numbers like that raise a question that sounds simple but isn't: **which came first, the gut or the worry?** By the end of this chapter you'll see that the honest answer is "often both," and you'll know how scientists figured that out.

11.2 A Two-Way Street

Before any technical terms, think about a friendship that's going badly. Jordan is rude to Casey, so Casey gets snappy, so Jordan gets ruder, so Casey gets snappier. If you only walk in at the end and see two people glaring at each other, you can't tell who started it. And maybe neither did: maybe they were both stressed from the same group project, and that hidden pressure made them both irritable.

That little scene holds the main ideas of this chapter. Effects can run one way, the other way, both ways at once, or come from a third thing pushing on both.

A **bidirectional relationship** is a connection between two things in which each one can influence the other, so that changes can flow in both directions. The gut-brain axis is the textbook example. In earlier chapters you saw the upward route (gut signals traveling through the vagus nerve, immune messengers, and microbial chemicals to the brain) and the downward route (stress hormones and nerve signals from the brain changing how the gut moves, senses, and defends itself). This chapter applies that two-way wiring to mood.

I'm a two-lane road



As a vagus nerve fiber, I carry messages both up and down, and so do the other gut-brain routes. So when gut problems and mood problems show up together, my first question is never "which one is to blame?" but "which lanes are busy right now?"

11.3 What Anxiety and Depression Mean

Everyone feels anxious or sad sometimes. Before a big test, a nervous stomach is normal. After a loss, sadness is normal. These feelings become a health problem when they are strong, last a long time, and get in the way of everyday life. For a deeper look at emotion circuits and psychiatric conditions in the brain, see From Neuron to Bedside, Chapter 11 and Chapter 15.

An **anxiety disorder** is a mental health condition in which worry, fear, or nervousness is more than occasional: it doesn't go away, shows up in many situations, and can get worse over time, interfering with daily life. That description follows the National Institute of Mental Health (NIMH), which lists several types, including generalized anxiety disorder, panic disorder, social anxiety disorder, and phobia-related disorders.

Major depressive disorder (often just called depression) is a mental health condition marked by a period of at least two weeks with a depressed mood or a loss of interest or pleasure in daily activities, along with other symptoms such as changes in sleep, appetite, energy, concentration, or feelings of self-worth.

NIMH's guide to teen depression lists signs that include often feeling sad, anxious, worthless, or "empty"; losing interest in activities; being easily irritated or angry; pulling away from friends and family; falling grades; changes in eating or sleeping; tiredness; and thoughts of suicide or self-harm. Depression is a real medical condition, not a character flaw or a lack of effort, and NIMH notes that it can be treated with talk therapy, medication, or both.

There is a third kind of worry that matters a lot in gut conditions. **GI-specific anxiety** is worry and fear focused specifically on gut sensations, gut symptoms, or the situations where they might happen, such as fearing a cramp in class, constantly scanning the body for signs of trouble, or avoiding trips where a restroom might be hard to reach. Researchers measure it with tools such as the Visceral Sensitivity Index, a 15-question scale developed and tested in 2004 by Labus and colleagues with 96 people with IBS.

GI-specific anxiety is different from general anxiety. Someone can be calm about school, friends, and the future, and still feel a spike of fear every time their stomach gurgles in a quiet classroom. It also connects to

Chapter 8: worry focused on gut sensations is one way the brain may turn up the pain volume.

Symptoms are not a diagnosis



Most of the big numbers in this chapter come from questionnaires that flag symptoms, not from a professional's diagnosis. "Screened positive for anxiety symptoms" and "has an anxiety disorder" are different claims, so watch which one a headline is making.

11.4 How Common Is It? Reading the Numbers

When two health conditions show up in the same person more often than chance would predict, doctors use a special word. **Psychiatric comorbidity** is the presence of a mental health condition, such as anxiety or depression, in a person who also has another health condition, such as IBD or IBS. ("Co" means together, and "morbidity" means illness.)

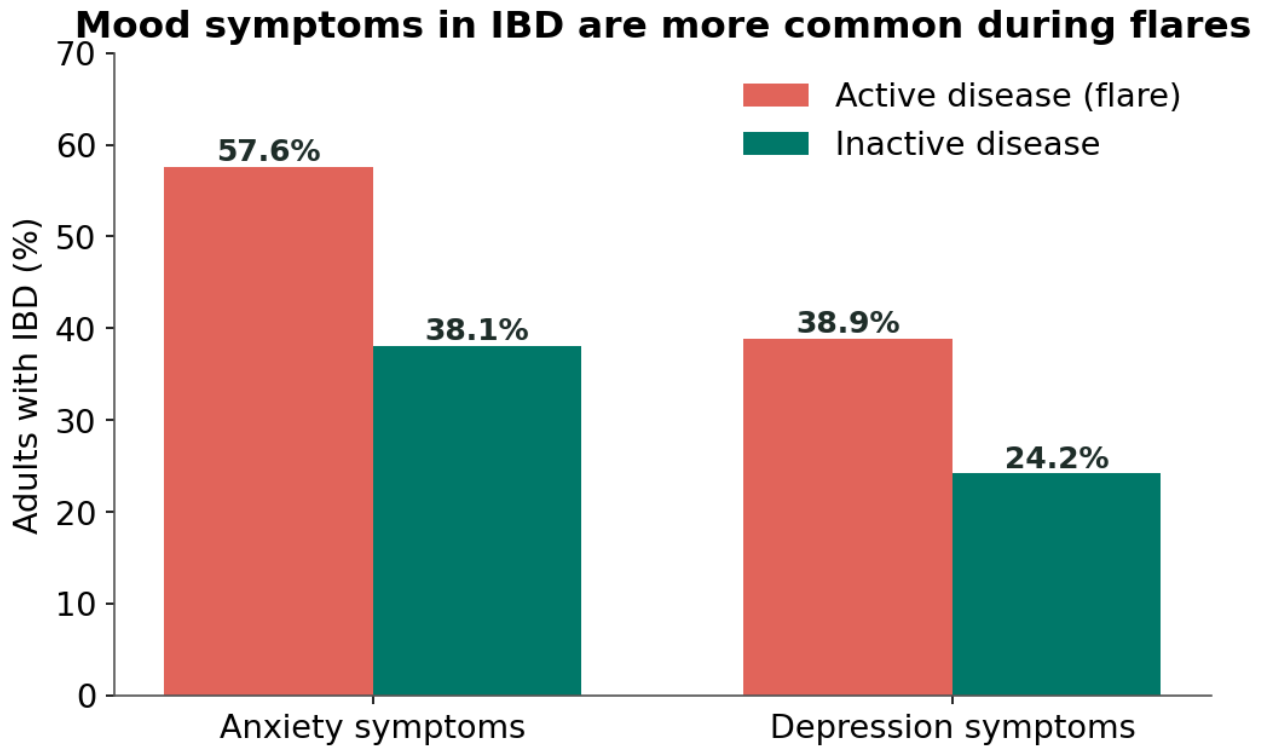
How do we know how common psychiatric comorbidity is in gut conditions? Two research tools do most of the work.

A **symptom questionnaire** is a standard set of questions, scored with fixed rules, that measures how many symptoms of a condition a person reports and how strong they are. A score above a set cutoff "screens positive." Questionnaires are fast and useful for spotting people who may need help, but they can't diagnose; that takes a full evaluation by a trained professional.

A **meta-analysis** is a study that uses statistics to combine the results of many earlier studies on the same question, giving a single pooled estimate that is usually more reliable than any one study alone. It is only as good as the studies that go into it.

Here is the most important meta-analysis for this chapter. In 2021, Barberio and colleagues pooled 77 studies that included 30,118 adults with IBD. Using screening questionnaires, they found:

- **Anxiety symptoms:** 32.1% (from 58 studies)
- **Depression symptoms:** 25.2% (from 75 studies)
- People with **active IBD** (a flare) had higher rates than people with inactive disease: anxiety symptoms 57.6% vs 38.1%, and depression symptoms 38.9% vs 24.2%. (These active-versus-inactive numbers come from a smaller subset of the studies.)
- People with Crohn's disease had slightly higher odds of both than people with ulcerative colitis, and women had higher rates of anxiety symptoms than men.



Source: Barberio et al. 2021, Lancet Gastroenterology & Hepatology (meta-analysis of 77 studies). Symptom questionnaires, not diagnoses; the active-versus-inactive numbers come from a subset of the studies.

These are symptom questionnaires, not diagnoses, and they come from adults. For IBS, a 2019 meta-analysis by Zamani and colleagues found anxiety symptoms in 39.1% and depression symptoms in 28.8% of people with IBS, about three times the odds seen in healthy people.

What about teens? A 2018 meta-analysis by Stapersma and colleagues pooled 28 studies of 8,107 children and teens with IBD (average age 14.3). It found anxiety symptoms in about 16.4% and depressive symptoms in about 15.0%, with lower rates of diagnosed anxiety disorders (4.2%) and depressive disorders (3.4%). These are lower than the adult numbers, but the authors warn that the studies used different questionnaires and cutoffs, so the figures should be read with caution. Studies with more active disease had higher rates of depressive symptoms, the same pattern seen in adults.

To put these numbers in context, mood struggles are common among all teens. In the 2025 Youth Risk Behavior Survey from the Centers for Disease Control and Prevention (CDC), published in October 2026, 33.3% of US high school students (about one in three, down from 39.7% in 2023) said that during the past year they had felt so sad or hopeless almost every day for two or more weeks in a row that they stopped doing some usual activities. That's not the same as having depression, but it shows that feeling this way is common and worth talking about, with or without a gut condition.

How to read a gut-brain claim: the 2021 IBD mood meta-analysis

Question	This study
Mouse or human?	Human. Adults with IBD only (no children or teens).
Correlation or cause?	Correlation. It pools observational studies that measured mood symptoms at one time, so it shows how common the symptoms are, not what causes them or which came first.
How many?	Large: 77 studies with 30,118 adults. But the studies differed a lot from each other, and the active-versus-inactive comparison used fewer studies.
How long?	Mostly snapshots. Each study measured symptoms once.
Who paid for it?	The paper's funding statement says "None."
Is something being sold?	No. The authors suggest that gastroenterologists screen for and treat anxiety and depression.

The careful conclusion: anxiety and depression symptoms are clearly common in adults with IBD, especially during flares, and that is a strong reason to check on mental health in IBD care. But this study alone can't tell us whether IBD causes the symptoms, the symptoms worsen IBD, or both. For that we need studies that follow people over time, which is where we go next.

Hype Meter: "People with IBD have higher rates of anxiety and depression symptoms"

Strong	Moderate	Preliminary	Hype

Verdict: Strong (as an association). A 2021 meta-analysis of 77 studies and 30,118 adults found anxiety symptoms in about a third and depression symptoms in about a quarter of people with IBD, with higher rates during active disease, and IBS shows a similar pattern. That analysis measured how common the symptoms are rather than comparing people with IBD to people without it. Studies that did make the comparison point the same way: in a 2023 Danish registry study of 22,103 people with IBD and 110,515 matched people without it, those with IBD were more likely to have hospital-recorded anxiety and depression, both before and for at least ten years after diagnosis, and a 2024 UK study of 3,898 children and young adults (ages 5 to 25) with IBD found more new diagnoses of depression and anxiety than in matched peers. For IBS, the 2019 meta-analysis found about three times the odds of anxiety and depression symptoms compared with healthy people. These are questionnaire symptoms, not diagnoses, and they describe a link, not a cause. **What would change the grade:** Very little would weaken the association itself. Large studies in teens using the same questionnaires would sharpen the picture for younger readers. (See the Hype Meter for what each grade means.)

11.5 Why a Link Is Not an Arrow

You met correlation vs causation in Chapter 3. Here we sharpen it with two more precise ideas, because gut-mood headlines so often go wrong right here.

Reverse causation is when the cause-and-effect arrow points the opposite way from the one assumed. If a study finds that people with depression have different gut bacteria, a headline might say "gut bacteria cause depression." But depression changes appetite, food choices, sleep, activity, and sometimes medicine use, and all of those can change gut bacteria. The arrow might run from mood to microbes, not the other way around.

A **confounding variable** is a third factor that affects both things being studied, creating a link between them even if neither causes the other. In the Jordan and Casey story, the stressful group project was a confounder. In gut-mood research, possible confounders include poor sleep, chronic pain, stressful life events, money worries, side effects of some medicines, and social isolation. Each of these could push both gut symptoms and mood in the same direction.

So how do scientists untangle the arrows? One of the best tools short of an experiment is to follow people over time. A **cohort study** is a study that follows a group of people (a cohort) over time, measuring things at the start and again later, to see which earlier factors predict later outcomes. If anxiety measured at the start predicts new gut problems years later, among people who didn't have gut problems at the start, that is evidence for a brain-to-gut direction. If gut problems at the start predict new anxiety later, among people who weren't anxious at the start, that is evidence for a gut-to-brain direction.

Cohort studies are powerful, but they still can't fully rule out confounders. A hidden factor present at the start could cause both later outcomes. That's why the strongest evidence for cause usually comes from

experiments, such as randomized trials, when those are possible and ethical.

The table below summarizes the three explanations for a gut-mood link we've just covered and what each would predict in a cohort study.

Explanation	What it means	What a cohort study would show
Gut to brain	Gut problems lead to later mood problems	Earlier gut symptoms predict later mood symptoms
Brain to gut (reverse causation, if the gut was assumed to be the cause)	Mood problems lead to later gut problems	Earlier mood symptoms predict later gut symptoms
Confounding	A third factor causes both	Both may move together; the cohort study alone may not tell

This is the hard part, and it pays off



Reverse causation and confounding take a while to click, so don't worry if you have to reread this section. Once you can spot them, you'll start catching the mistake in health headlines.

11.6 Evidence That the Street Runs Both Ways

Now for the real studies that followed people over time.

A 12-year study in Australia. In 2012, Koloski and colleagues reported on a random sample of 1,775 adults in Australia who answered a survey about gut symptoms, anxiety, and depression in 1997. Twelve years later, 1,002 of them answered again. Two findings stood out:

- Among people who had no functional gut disorder at the start, higher anxiety at the start predicted developing a new functional gut disorder (such as IBS or functional dyspepsia) 12 years later. That's the brain-to-gut direction.
- Among people who did not have high anxiety or depression at the start, those who had a functional gut disorder at the start had higher anxiety and depression 12 years later. That's the gut-to-brain direction.

The authors concluded that the brain and gut interact in both directions in these disorders. This is a human cohort study, so it shows prediction over time, not proof of cause, and 773 of the original 1,775 people (more than 4 in 10) didn't complete the follow-up survey.

A 2-year study of IBD in England. In 2018, Gracie and colleagues followed 405 adults with Crohn's disease or ulcerative colitis for at least two years, measuring anxiety and depression with a questionnaire and tracking flares, steroid prescriptions, hospital stays, and changes in treatment.

- People whose IBD was **active** at the start were almost six times as likely to develop abnormal anxiety scores later (a hazard ratio of 5.77, meaning their risk was about 5.77 times higher over the follow-up). That estimate is rough, though: the range of likely values ran from about 2 to 18 times higher.
- Among people whose IBD was **quiet** at the start, those with abnormal anxiety scores were about twice as likely to later need steroids or have a flare (hazard ratio 2.08), and more likely to need their treatment stepped up.

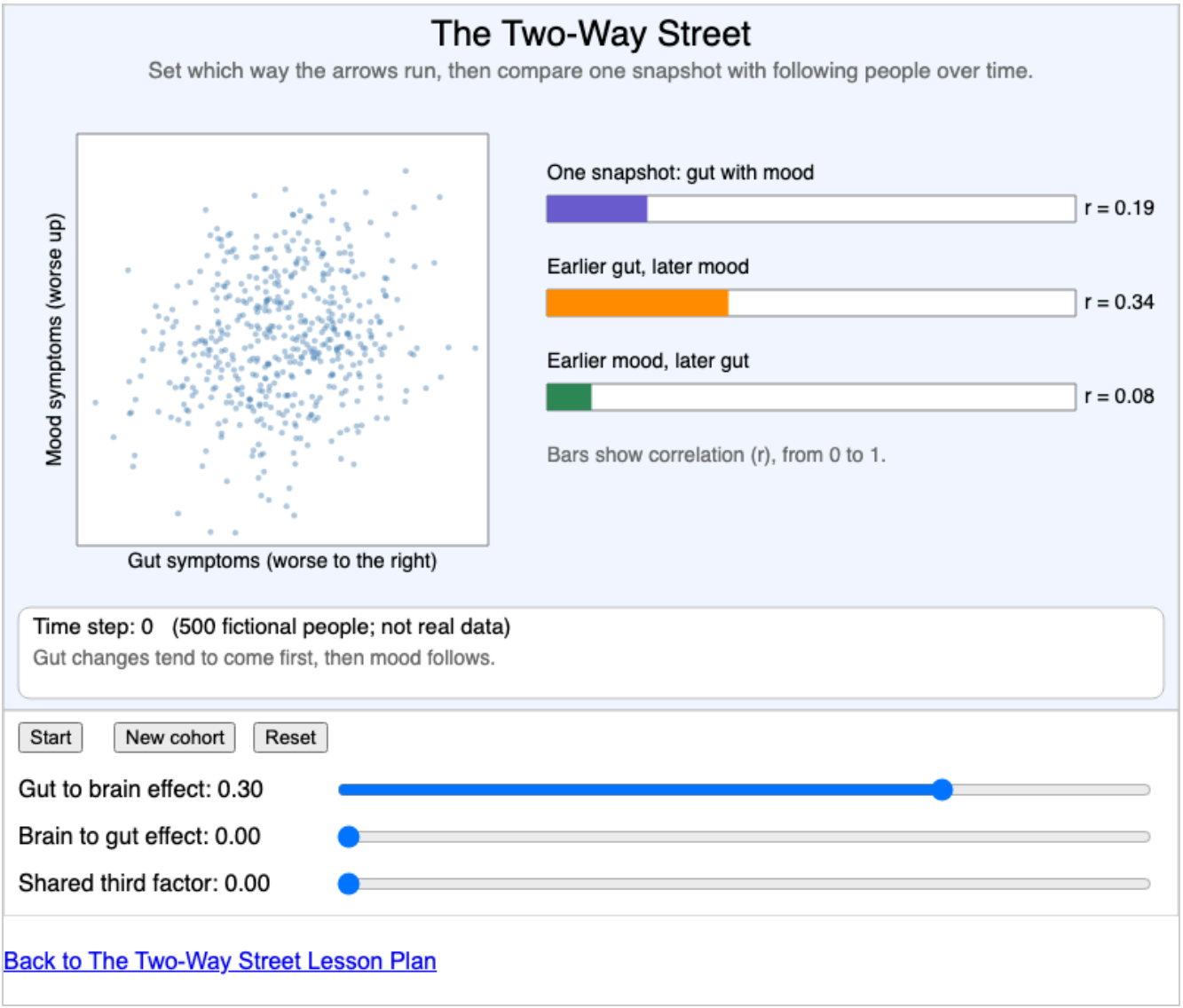
These links held even when the researchers used a stool test of gut inflammation to confirm that the disease was truly quiet at the start. Again, it's a cohort study, so confounders can't be completely ruled out, but it's strong evidence that in IBD, gut activity and mood each predict changes in the other.

This brings us back to Riya. Her pre-flare anxiety might be partly an early signal of a flare already brewing (gut to brain), partly a stressor that nudges her immune system and gut toward a flare (brain to gut), or both. None of this means anxiety caused her Crohn's disease. These studies are about how symptoms and flares change over time in people who already have a condition, not about what causes IBD to start. (Chapter 9 covers what is known about IBD's causes.)

11.7 Try It: The Two-Way Street

The simulation below follows 500 fictional people. Each dot is one person, placed by their gut-symptom score (left to right) and mood-symptom score (bottom to top). You set the hidden rules: how strongly gut symptoms change later mood (gut to brain), how strongly mood changes later gut symptoms (brain to gut), and how strongly a shared third factor (a confounder) pushes on both. The top bar shows the correlation in one snapshot, like a survey. The other two bars show what you'd see in a cohort study: how well earlier gut symptoms predict later mood, and how well earlier mood predicts later gut symptoms. A correlation (r) of 0 means no link and 1 means a perfect link.

Diagram: The Two-Way Street



Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch11-two-way-street/main.html

Open The Two-Way Street fullscreen

MicroSim specification: The Two-Way Street

Type: microsim **sim-id:** ch11-two-way-street
Library: p5.js
Status: Implemented
Bloom Level: Analyze
Bloom Verb: analyze, distinguish
Learning Objective: The learner will explain why gut-to-brain effects, brain-to-gut effects, and a shared confounder can each produce a similar correlation at one time point, and analyze how following people over time helps detect direction (reverse causation) but cannot by itself rule out confounding.

Canvas: 480 px drawing area plus 140 px controls (iframe 622 px); responsive to about 380 px wide, with the bars moving below the scatter plot on narrow screens.

Controls: Start/Pause, New cohort, Reset; Gut to brain effect slider (0 to 0.4, step 0.05, default 0.3); Brain to gut effect slider (0 to 0.4, default 0); Shared third factor slider (0 to 0.4, default 0).

Rules: 500 simulated people with gut score G, mood score M, and a fixed hidden trait Z. Each time step: G' = 0.5G + (brain to gut)M + (third factor)Z + noise; M' = 0.5M + (gut to brain)G + (third factor)Z + noise (noise SD 0.7). The cohort is run 40 steps to settle whenever a slider changes. Bars show the Pearson correlation of G and M now, of earlier G with later M, and of earlier M with later G.

Feedback: A readout names the pattern: gut first, mood first, linked with no clear order (both directions or a shared cause), or almost no link.

Provenance: Sections 11.5 and 11.6 (Koloski 2012; Gracie 2018). All numbers are simulated teaching values, not data from any study.

Start with the default settings: gut to brain at 0.30 and everything else at 0. The snapshot shows a modest link (around r = 0.2), and the "earlier gut, later mood" bar is clearly longer than "earlier mood, later gut." Now flip it: set gut to brain to 0 and brain to gut to 0.30. The snapshot bar looks about the same as before. A single survey can't tell these two worlds apart, which is exactly the reverse causation problem. But the time bars swap, so following people over time can.

Next, set both directions to 0.15. The snapshot still shows a link, and the two time bars come out about equal: a true two-way street. Finally, set both directions to 0 and the shared third factor to 0.30. The snapshot link gets even stronger, yet nothing in the model connects gut and mood directly. Both time bars are long and equal, so even a cohort study can't tell a two-way street from a hidden shared cause without measuring that cause. Press **New cohort** a few times to see how much the numbers wobble by chance, even with 500 people.

What this model leaves out

- Real people have many gut and mood symptoms, not one score each, and the strength of effects differs from person to person.
- Real effects may be delayed, may build up over months, or may only appear during flares; the sim uses one simple step.
- Real studies have dropouts, measurement error, and many confounders at once, not one hidden trait.
- Treatment, which changes both gut and mood symptoms, is left out completely.
- All numbers are made up. The sim shows how study designs behave, not what real effect sizes are.

11.8 Gut to Brain: How Gut Problems Can Affect Mood

If gut problems can lead to mood problems, how? There are several routes, and they likely work together.

The weight of living with it

The first route is the most obvious and the easiest to overlook. **Illness burden** is the total load that a health condition places on a person's life, including symptoms such as pain, urgency, and fatigue, along with missed school or work, medical appointments, treatment side effects, money costs, worry about the future, and effects on friendships and self-image. A long-lasting gut condition carries a heavy illness burden. Imagine planning every outing around restrooms, missing a concert because of a flare, or being the only person at a sleepover who can't eat the pizza. Anyone carrying that load could become anxious or low.

Illness burden helps explain why mood symptoms are more common during active disease, when the burden is heaviest. It also explains why the answer is never "just think positive." The stress is real, and it deserves real support.

Inflammation and the brain

The second route is biological. In Chapter 4 you learned about sickness behavior, the tiredness, low mood, and withdrawal that come with infections, driven by immune messengers called cytokines reaching the brain. The **inflammatory depression theory** is the idea that ongoing inflammation in the body, signaled to the brain by cytokines and other immune messengers, can push brain circuits toward depression-like changes in mood, energy, and motivation, at least in some people.

What's the evidence? In 2020, Osimo and colleagues combined 107 studies comparing 5,166 people with depression and 5,083 people without it. On average, people with depression had higher blood levels of several inflammation markers, including C-reactive protein (CRP), interleukin-6, and tumor necrosis factor. The authors called depression "a pro-inflammatory state." But this was an average shift across the group, not a feature of

every depressed person, and no blood test can diagnose depression. It also measures blood markers at one time, so it can't show whether inflammation came first.

A 2016 review by Miller and Raison lays out the theory's logic: immune signals that once helped early humans survive infections and threats (by making them withdraw, rest, and stay alert) may, in modern life, help drive depression in some people. They describe this as a promising treatment target still being tested. Since IBD is a disease of gut inflammation, this theory is one possible reason mood symptoms rise during flares. It's a hypothesis with good supporting evidence for the link, but cause in humans is not settled.

Microbes and mood

The third route is the one that gets the most headlines. Could gut microbes themselves affect mood? Scientists test this with a **microbiota transfer study**, an experiment in which gut microbes (usually from stool) from one group of people or animals are transferred into animals whose own gut microbes have been removed or depleted, to see whether traits move along with the microbes.

Two well-known studies did this in 2016:

- Kelly and colleagues in Ireland collected stool from people with major depression and from healthy people. Microbes from the depressed group, transferred into rats whose gut microbes had been depleted, led the rats to show behaviors that researchers read as depression-like and anxiety-like (such as anhedonia, a loss of interest in rewards), plus changes in how they processed tryptophan.
- Zheng and colleagues in China moved gut microbes from people with major depression into germ-free mice (mice raised with no microbes, which you met in Chapter 3). These mice showed more depression-like behavior than mice that received microbes from healthy people.

These are real experiments that test cause, but in rodents. Rodent behavior tests can't capture human feelings, the transfers involve whole communities of microbes (so we don't know which ones matter), and rodents raised without microbes are very unusual animals. The studies suggest microbes *can* influence behavior. They don't show that microbes cause depression in people.

Human studies so far show links, not cause. In 2019, Valles-Colomer and colleagues studied the gut microbes of 1,054 people in Belgium's Flemish Gut Flora Project and checked their results in a separate group. People with depression had lower levels of certain bacteria (Coprococcus and Dialister), even after accounting for antidepressant use. But this was a one-time snapshot. Depression changes diet, sleep, and activity, all of which change gut bacteria, so reverse causation is very possible.

Hype Meter: "Gut bacteria from depressed people cause depression"

Strong	Moderate	**Preliminary**	Hype

Verdict: Preliminary. In 2016, two animal studies found that moving gut microbes from people with major depression into rats or germ-free mice led to depression-like behavior. Human studies show that people with depression have somewhat different gut bacteria, but these are snapshots that can't show direction. That microbes can change rodent behavior is reasonably supported; that they cause depression in people is not shown. **What would change the grade:** Long-term human cohort studies showing microbe changes come before depression, plus well-controlled human trials in which changing the microbes changes mood, would move it up.

11.9 Brain to Gut: How Mood Can Affect the Gut

Now the downward lane. You already know most of these routes from earlier chapters.

- **Stress hormones and nerves.** In Chapter 7 you saw how the HPA axis and the stress response change gut movement, sensitivity, the gut barrier, and immune cells such as mast cells. Anxiety keeps these systems switched on more often.
- **Pain amplification.** In Chapter 8 you saw how worry and attention can turn up pain through descending pathways. GI-specific anxiety is a direct route: the more a person fears gut sensations, the louder those sensations may become.
- **Daily life.** Depression can drain energy and motivation, making it harder to keep up with sleep, meals, activity, and appointments. These everyday changes can affect how a person feels physically, though researchers are still sorting out how much each one matters for gut conditions.

In IBD, the Gracie study suggests that anxiety in people whose disease is quiet predicts later flares and treatment changes. Scientists don't yet know exactly how. It could involve stress effects on the immune system, changes in behavior, or confounders the study didn't measure. That is why the careful phrase is "anxiety predicts later flares," not "anxiety causes flares." And once more: none of this says anxiety or stress causes IBD to begin.

In IBS, the brain-to-gut lane is especially busy, which is part of why brain-gut therapies such as CBT and gut-directed hypnotherapy help many people (see Chapter 10).

11.10 "Fix Your Gut, Fix Your Mood"? Grading the Big Claim

Put the evidence together and a popular claim falls apart. Wellness posts often say that healing your gut, with a supplement, a cleanse, a special diet, or a probiotic, will fix depression or anxiety. Some posts go further and tell people they don't need therapy or medicine.

Here's what this chapter shows. Yes, the gut-brain link is real and runs both ways. Yes, inflammation and microbes may play a role in some people's mood. But the microbe evidence is mostly from animals and snapshots, and depression and anxiety have many causes, including genes, life events, stress, and brain circuits that have nothing to do with the gut.

For people with IBD, treating inflammation is important for many reasons, but studies show mood symptoms remain common even in inactive disease (24.2% for depression symptoms in Barberio's analysis), so gut treatment alone isn't enough for everyone. Probiotics and depression are covered in Chapter 16, where you'll see that the trial evidence is small and mixed.

Hype Meter: "Fixing your gut will fix your depression"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. The gut-mood link is real and two-way, but the evidence that gut changes cause human depression comes mostly from rodent transfer studies and one-time snapshots. Depression has many causes, mood symptoms stay common even when IBD is inactive, and proven treatments (talk therapy, medication, or both) work on the brain directly. Promising that gut fixes will cure depression can lead people to delay care that works. **What would change the grade:** Large, long, well-controlled human trials showing that a specific gut treatment reliably relieves depression, compared with placebo, could support a narrower claim for some groups of people.

Both lanes need care



If the street runs both ways, help can come from both ends too. Treating gut symptoms can ease mood, and treating anxiety or depression can ease gut symptoms, so the best plans usually work on both at once.

11.11 Getting Help

Knowing that gut conditions and mood are linked matters most if it helps people get care. The last three ideas of the chapter are about exactly that.

Asking for help

Help-seeking is the process of recognizing that you're struggling and reaching out for support, whether to a friend, family member, school counselor, doctor, or mental health professional. It sounds simple, but it's often the hardest step. People with gut conditions may already feel worn out from explaining their bodies, and some worry that mentioning anxiety will make doctors take their gut symptoms less seriously. Others come from

families or cultures where mental health is rarely discussed. (Chapter 19 looks at culture and stigma in more depth.)

NIMH's guide for teens suggests talking to a trusted adult, such as a parent, teacher, or school counselor, and asking a doctor about professional help. It also suggests staying connected with friends and family even when you don't feel like it, staying active, and keeping a regular sleep schedule. Telling your gastroenterologist about mood symptoms is not a distraction from your gut care. It's part of it, as the next ideas show.

Help right now

Crisis resources are services that give immediate, free support to someone in emotional distress or danger, such as suicide and crisis hotlines, text lines, and emergency rooms. In the US, the 988 Suicide & Crisis Lifeline launched in July 2022. You can call or text 988, or chat at 988lifeline.org. It is free, confidential, and available 24 hours a day, 7 days a week. If someone is in immediate danger, call 911.

If you are struggling right now

If you are thinking about suicide or are in crisis, call or text **988** to reach the 988 Suicide & Crisis Lifeline (in the US), or go to the nearest emergency room. Outside the US, you can find a helpline at findahelpline.com. You can also talk to a parent, school counselor, or doctor.

Care that treats the whole person

Integrated care is an approach in which physical and mental health care are delivered together by a coordinated team, for example a gastroenterologist, nurse, dietitian, and psychologist who share information and plan care as one team, often in the same clinic. Instead of sending someone with IBD and depression to two separate systems that never talk, integrated care treats both as parts of one problem.

What's the evidence? In 2023, Riggott and colleagues (the same Leeds research group behind the Gracie studies) updated their earlier 2017 analysis and pooled 25 randomized trials of psychological therapy in people with IBD aged 16 and up. In people whose disease was quiet, therapy lowered anxiety, depression, and stress scores and improved quality of life by small amounts at the end of treatment, and a small benefit for depression scores lasted to the end of follow-up. But therapy didn't change disease activity or prevent flares, and all 25 trials had a high risk of bias. Benefits were largest in trials that enrolled people who were already struggling with their mood, fatigue, or quality of life.

A 2025 Cochrane review of 48 trials reached a similar conclusion: in adults, psychological care probably improves mood and quality of life slightly, and it may have little to no effect on disease activity. In other words, therapy helps some people's mood and quality of life, but it isn't a treatment for the inflammation itself.

Barberio's 2021 meta-analysis and Gracie's 2018 cohort study both concluded that people with IBD should be checked for anxiety and depression as part of routine care.

For families

If a teen with a gut condition seems more irritable, withdrawn, or tired than usual, it may be the illness, mood, or both, and it's worth asking gently. Try "You've seemed down lately. Do you want to talk, or should we bring it up with your doctor?" rather than "You just need to stay positive." Avoid suggesting that worrying caused their condition; that isn't what the science shows, and it adds guilt. You can help by mentioning mood at gut appointments and by learning the warning signs of depression and the 988 Lifeline yourself.

If you're going through this

Feeling anxious or low when you have a gut condition is common, and it's not a sign of weakness or that you're "not handling it." It's also not your fault that your gut acts up when you're stressed. Try telling your GI doctor or nurse something like "My mood has been really low since my last flare." Saying it out loud to your care team is how integrated care starts, and many clinics can connect you with someone who understands both the gut and the mind.

At the Bedside: A Flare That Took More Than the Gut

Meet the patient (fictional)

Marcus is 16 and a sophomore who plays bass in a garage band and loves basketball. He was diagnosed with ulcerative colitis a year ago. Last winter he had a bad flare with bloody diarrhea, urgency, and exhaustion, and he missed three weeks of school. The flare is now under control, but his mom notices he still isn't himself. He's stopped going to band practice, sleeps most of the afternoon, snaps at his little sister, and says "What's the point?" when asked about the basketball tryouts he was once excited about.

What the doctor checks: At a follow-up visit, his gastroenterologist first makes sure the colitis is truly calm: she reviews his symptoms and checks blood and stool tests for inflammation, which are much better. She then talks with Marcus alone for a few minutes and asks him to fill out a short screening questionnaire for depression and anxiety. His depression score is high. She also asks directly, and kindly, whether he has had thoughts of hurting himself. He says no, and she makes sure he and his mom know about 988.

Connecting the signals: Marcus's mood dropped during his flare, when his illness burden was heaviest and his gut was inflamed. That fits the gut-to-brain lane: inflammation may have affected his brain, and weeks of pain, isolation, and missed school added stress. But his mood stayed low even after the inflammation calmed, which suggests the depression is no longer just a result of the flare. His team also knows the brain-to-gut lane: untreated depression could make it harder for him to keep up with daily routines and treatment, and in adults with IBD, anxiety has been linked to later flares.

Diagnosis: Ulcerative colitis in remission, with symptoms of depression. The team refers Marcus to a psychologist for a full evaluation, which confirms major depressive disorder.

Why it happens: Psychiatric comorbidity is common in IBD, especially during and after active disease. Likely contributors include the illness burden of a severe flare, inflammation signaling to the brain (the inflammatory depression theory), and the social losses of missing school and activities. Because the link is bidirectional, treating his depression matters for his colitis too.

The mind-body side: Marcus admits he felt embarrassed to bring up his mood at a "gut appointment." His doctor tells him this is one of the most common things she sees and that it's part of his IBD care. The team includes a psychologist who works with teens with chronic illness. Marcus and his parents meet with the school counselor to plan his catch-up work and a quiet return to band.

Treatment today: Marcus continues his colitis treatment as prescribed by his gastroenterologist. For depression, treatment options include talk therapy such as cognitive behavioral therapy, medication prescribed and monitored by a doctor, or both, as NIMH describes. His GI doctor and psychologist share notes so that his whole care team knows how both his gut and his mood are doing. Any decisions about medicines belong to Marcus, his family, and his doctors.

What's new in research: In 2021, Lores and colleagues reported on a hospital IBD service in Australia that screened 335 adults for mental health risk and offered psychological care to those at risk. Among people who accepted the care, emergency department visits dropped in the following year, and the program saved money over two years. **Evidence grade: Preliminary.** It was a single-center study without a randomized comparison group, in adults, so other changes over time could explain part of the drop.

Your turn: reason through a variation

Riya has been in remission for a year, but she has started feeling intensely nervous before every orchestra concert. She worries that her stomach will act up on stage, and she has begun skipping meals on concert days and checking where the nearest restroom is. She isn't sad, and she enjoys school otherwise. What is going on, and what might help?

Answer: This sounds most like GI-specific anxiety: fear focused on gut symptoms and the situations where they might happen, rather than general anxiety or depression. It's understandable after years of unpredictable symptoms, and it's worth taking seriously, because fear of gut sensations can turn up gut pain and symptoms through the brain-to-gut lane. Her care team would want to confirm her Crohn's is still quiet, and could then connect her with a psychologist who works with gut conditions. CBT-based approaches target exactly this kind of worry.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Anxiety or stress causes IBD.
Reality: Studies show that anxiety in people who already have IBD predicts later flares, and active IBD predicts later anxiety. These are about how symptoms change over time, not about what makes IBD start. No study in this chapter shows that anxiety causes IBD to begin.

Myth: Depression in people with IBD is just a normal reaction to being sick, so it doesn't need treatment.
Reality: Feeling down about an illness is understandable, but major depressive disorder is a real condition that can be treated, and it may affect the gut through the brain-to-gut lane. Researchers recommend screening for and treating anxiety and depression as part of IBD care.

Myth: Since people with gut conditions have more depression, the gut must be causing it.
Reality: A link can come from gut to brain, brain to gut, both, or a confounding variable such as poor sleep or pain. Cohort studies suggest the street runs both ways.

Myth: You should keep mental-health struggles to yourself at GI appointments, because your doctor will think your symptoms are "all in your head."
Reality: Telling your gastroenterologist about mood symptoms helps them treat you as a whole person. Mood problems don't make gut symptoms less real, and many IBD clinics now include mental health care.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Depression starts in the gut! Studies prove that people with depression have bad gut bacteria, so our 30-day gut reset will fix your mood."

Grade: Hype. Human studies such as the 2019 Flemish Gut Flora Project found that people with depression had lower levels of some bacteria, but these were snapshots that can't show direction, and depression itself changes diet, sleep, and activity, which change gut bacteria (reverse causation). Animal transfer studies suggest microbes can influence behavior, but that's Preliminary for humans. No evidence in this chapter supports a 30-day product fixing depression. A careful version: "People with depression tend to have somewhat different gut bacteria, and scientists are studying whether microbes play a role. Talk therapy and medication are proven treatments."

2. Predict: In a new cohort study, 1,000 teens with IBD fill out mood questionnaires every 6 months for 3 years. Based on this chapter, what two patterns would you predict, and why?

Teens with active IBD at one visit should be more likely to report new anxiety or depression symptoms at later visits (gut to brain, through inflammation and illness burden), and teens with quiet IBD but high anxiety should be more likely to have flares later (brain to gut). This prediction comes from adult cohort studies (Gracie 2018) and the 12-year Koloski study, so a teen study would test whether the same two-way pattern holds at younger ages.

3. Explain: Why might mood symptoms be more common during an IBD flare than during remission?

During a flare, inflammation is high, and cytokines can signal the brain and push it toward sickness behavior and depression-like changes (the inflammatory depression theory). The illness burden is also heaviest: more pain, urgency, fatigue, missed school, and social isolation. Stress and worry about the flare can add to it too. Barberio's meta-analysis found anxiety symptoms in 57.6% of people with active IBD compared with 38.1% with inactive disease.

4. Apply: A study finds that teens who drink more energy drinks report more stomachaches and more anxiety. A classmate concludes, "Stomachaches make you anxious." Name a confounding variable and a reverse-causation explanation.

A confounder could be poor sleep or school stress: teens who sleep badly or are under pressure may drink more energy drinks, and the same lack of sleep or stress could cause both stomachaches and anxiety. Reverse causation: anxiety could cause the stomachaches (brain to gut), rather than the other way around. The energy drinks themselves might also contribute to both. A cohort study or an experiment would be needed to sort these apart.

5. Read the data. In the 2021 Barberio meta-analysis of adults with IBD, researchers compared mood symptoms in people with active versus inactive disease (from a subset of the 77 studies):

Group	Anxiety symptoms	Depression symptoms
Active IBD (flare)	57.6%	38.9%
Inactive IBD	38.1%	24.2%

5. What does this data show, and what can't it show?

It shows that mood symptoms are more common during active disease: anxiety symptoms are about 20 percentage points higher, and depression symptoms about 15 points higher. It also shows that mood symptoms are common even when IBD is inactive. It can't show direction: active disease could worsen mood, or poor mood could come before flares, or both (and these are snapshots). It can't diagnose, because these are questionnaire symptoms, and it can't be applied directly to teens. A useful follow-up: a cohort study that measures inflammation and mood repeatedly in the same people, like Gracie 2018, ideally in teens.

Exercises

Remember

1. What is the difference between screening positive on a symptom questionnaire and being diagnosed with an anxiety disorder?

Answer

A symptom questionnaire counts reported symptoms and flags people whose scores are above a cutoff. A diagnosis of an anxiety disorder requires a full evaluation by a trained professional who checks how long the symptoms have lasted, how much they interfere with life, and whether something else explains them.

1. Name the 24/7 crisis line in the US and three ways to reach it.

Answer

The 988 Suicide & Crisis Lifeline. You can call 988, text 988, or chat at 988lifeline.org. It's free and confidential. If someone is in immediate danger, call 911.

Understand

1. Explain the difference between reverse causation and a confounding variable, using gut symptoms and anxiety as your example.

Answer

Reverse causation means the arrow runs the opposite way from what was assumed: for example, a study assumes gut symptoms cause anxiety, but really anxiety causes gut symptoms. A confounding variable is a third factor, such as poor sleep or chronic stress, that causes both gut symptoms and anxiety, making them appear linked even if neither causes the other.

1. Explain why a cohort study gives better evidence about direction than a one-time survey.

Answer

A cohort study measures people at the start and again later, so it can test whether one thing measured earlier predicts the other thing appearing later. A one-time survey only shows that two things occur together, which can happen whichever direction the effect runs. Cohort studies still can't fully rule out confounders.

Apply

1. Using The Two-Way Street MicroSim, find settings where the snapshot correlation is about 0.2 in two different ways. Record the three bar values for each, and explain which study design could tell your two

settings apart.

2. A friend with IBS says, "My doctor sent me to a psychologist, so she must think my IBS is fake." Using the idea of a bidirectional relationship and integrated care, write three or four sentences you could say to reassure them.

Analyze

1. Compare the Koloski 2012 study and the Gracie 2018 study. For each, identify the population, how long people were followed, and which directions of effect it supported. What can neither study fully rule out?
2. Analyze the two 2016 microbiota transfer studies using the six questions (mouse or human, correlation or cause, how many, how long, who paid, is something being sold). Which questions can you answer from the chapter, and which would you need the full papers for? Why do they earn only a Preliminary grade for human depression?

Evaluate

1. A school is deciding whether to add a mental health screening question to the forms that students with chronic illnesses fill out for the nurse. Evaluate the benefits and risks of this plan, using at least two pieces of evidence from this chapter.
2. Evaluate the inflammatory depression theory. Using the Osimo 2020 meta-analysis and the Miller and Raison 2016 review, decide what grade the claim "inflammation causes depression" deserves, and what grade "people with depression have higher inflammation markers on average" deserves. Explain why they differ.

Create

1. Design a cohort study to test whether GI-specific anxiety in teens with IBS predicts worse pain a year later. Describe who you would recruit, what you would measure and when, one confounding variable you would measure, and the result that would support your hypothesis.
2. Create a short, friendly card (under 150 words) that a pediatric IBD clinic could hand to teens, explaining why the clinic asks about mood, what the two-way street means, and where to get help right away (including 988).

Key Takeaways

- Anxiety and depression symptoms are common in gut conditions. In adults with IBD, about a third screen positive for anxiety symptoms and a quarter for depression symptoms, with higher rates during flares. These are questionnaire symptoms, not diagnoses.

- Anxiety disorders, major depressive disorder, and GI-specific anxiety are different things. GI-specific anxiety focuses on gut sensations and the situations where they might happen.
- A link between gut and mood problems is not an arrow. It can reflect gut-to-brain effects, brain-to-gut effects (reverse causation, if you assumed the other direction), both, or a confounding variable.
- Cohort studies that follow people over time, such as a 12-year Australian study and a 2-year IBD study, show that the gut-brain street runs both ways. They still can't fully rule out confounders.
- Possible gut-to-brain routes include illness burden, inflammation (the inflammatory depression theory), and microbes, though microbiota transfer studies are in animals and grade Preliminary for humans. "Fixing your gut will fix your depression" is Hype.
- Help-seeking is part of good gut care. Integrated care treats gut and mental health together, and crisis resources such as the 988 Lifeline (call, text, or chat) are free, confidential, and available 24/7.

You learned to read the arrows!



You can now look at a gut-mood headline and ask the right questions: which way does the arrow point, what else could explain it, and was anyone followed over time? Next, in Chapter 12, we'll explore celiac disease and food reactions, where one specific food protein sets off an immune attack on the gut.

Quiz: Anxiety, Depression, and the Gut

Test your understanding of Chapter 11. Choose the best answer, then click **Show Answer** to check.

Question 1

What does "psychiatric comorbidity" mean?

A. A mental health condition caused directly by gut bacteria

B. A medicine that treats both the gut and the brain

C. A mental health condition occurring in a person who also has another health condition

D. A doctor who specializes in both psychiatry and gastroenterology

Show Answer

The correct answer is **C**. Psychiatric comorbidity means having a mental health condition, such as anxiety or depression, alongside another health condition, such as IBD or IBS. It describes things occurring together and says nothing about cause, so option A adds a causal claim the term doesn't make.

Concept Tested: Psychiatric Comorbidity **Bloom's Level:** Remember

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Question 2

According to the 2021 Barberio meta-analysis of 30,118 adults with IBD, about what share screened positive for anxiety symptoms?

A. About one in three

B. About one in ten

C. About nine in ten

D. About one in a hundred

Show Answer

The correct answer is **A**. The pooled prevalence of anxiety symptoms was 32.1%, about one in three, and depression symptoms were 25.2%, about one in four. These were questionnaire symptoms, not diagnosed disorders, and the study included adults only.

Concept Tested: Meta-Analysis **Bloom's Level:** Remember

Question 3

Which example best describes GI-specific anxiety?

A. Feeling sad and losing interest in hobbies for several weeks

B. Worrying about many everyday things, such as grades, friends, and the future

C. Sudden panic attacks that come with no warning in any situation

D. Fear focused on gut sensations, such as dreading a cramp in class and always checking where the restroom is

Show Answer

The correct answer is **D**. GI-specific anxiety is worry focused on gut symptoms and the situations where they might happen. Option B describes general, wide-ranging worry, which is different: someone can be calm about school and friends and still fear gut sensations.

Concept Tested: GI-Specific Anxiety **Bloom's Level:** Remember

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Question 4

Why can't a high score on a symptom questionnaire, by itself, diagnose an anxiety disorder?

A. Questionnaires are only used in mouse studies

B. A questionnaire flags reported symptoms above a cutoff, while a diagnosis needs a full evaluation by a trained professional

C. Questionnaire scores are always higher in people with IBD, so they are meaningless

D. Anxiety disorders can only be diagnosed with a blood test

Show Answer

The correct answer is **B**. Questionnaires are quick screening tools that count symptoms; a diagnosis checks how long symptoms last, how much they interfere with life, and whether something else explains them. Option D is wrong: there is no blood test for anxiety disorders or depression.

Concept Tested: Symptom Questionnaire **Bloom's Level:** Understand

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Question 5

A study finds that people with depression have lower levels of certain gut bacteria. Which explanation is an example of reverse causation?

A. Depression changes appetite, food choices, and sleep, which then change the gut bacteria

B. The low levels of bacteria cause the depression

C. Poor sleep separately causes both depression and the bacteria change

D. The bacteria and depression are linked by pure chance

Show Answer

The correct answer is **A**. The headline usually assumes bacteria cause depression; reverse causation means the arrow runs the other way, from depression to the bacteria. Option C describes a confounding variable (a third factor causing both), which is a different problem.

Concept Tested: Reverse Causation **Bloom's Level:** Understand

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Question 6

A 2020 meta-analysis found that, on average, people with depression have higher blood levels of inflammation markers such as CRP and interleukin-6. What is the best interpretation?

A. Every person with depression has high inflammation

B. A blood test for CRP can now diagnose depression

C. It supports the inflammatory depression theory as a link, but it shows an average shift and does not prove inflammation came first

D. It proves that inflammation from the gut is the only cause of depression

Show Answer

The correct answer is **C**. The study showed a group-level shift in inflammation markers, which fits the theory that inflammation can push the brain toward depression in some people. But it measured blood at one time, so it can't show direction, and it doesn't apply to every individual. Option B is wrong because no blood test diagnoses depression.

Concept Tested: Inflammatory Depression Theory **Bloom's Level:** Understand

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Question 7

Riya wants to know whether her anxiety tends to come before her Crohn's flares or after them. Which study design would best answer that question for people like her?

A. A one-time survey of anxiety in 5,000 people with Crohn's disease

B. A cohort study that measures anxiety and disease activity in the same people repeatedly over two years

C. A study that moves gut microbes from people with Crohn's disease into germ-free mice

D. A survey that asks people whether they think anxiety causes Crohn's

Show Answer

The correct answer is **B**. Following the same people over time lets researchers see whether anxiety measured earlier predicts flares later, and whether flares predict later anxiety, as the 2018 Gracie study did. Option A is large but is a single snapshot, so it can show that the two occur together but not which comes first.

Concept Tested: Cohort Study **Bloom's Level:** Apply

Question 8

A survey finds that students who sleep less than 6 hours a night report both more stomachaches and more anxiety. A classmate says, "Stomachaches must cause anxiety." What role does sleep most likely play here?

A. It is the outcome being measured

B. It proves the stomachaches cause anxiety

C. It is an example of a microbiota transfer study

D. It is a possible confounding variable that could cause both stomachaches and anxiety

Show Answer

The correct answer is **D**. Short sleep could worsen both gut symptoms and anxiety, creating a link between them even if neither causes the other. Option B gets it backward: a third factor that affects both makes it harder, not easier, to conclude that one causes the other.

Concept Tested: Confounding Variable **Bloom's Level:** Apply

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Question 9

In a 12-year Australian cohort study, anxiety at the start predicted new functional gut disorders later, and gut disorders at the start predicted higher anxiety and depression later. What does this pattern best support?

A. A bidirectional relationship between the brain and the gut

B. Proof that anxiety causes all gut disorders

C. Proof that gut disorders cause all anxiety

D. That gut symptoms and anxiety are unrelated

Show Answer

The correct answer is **A**. Each direction predicted the other over time, which is the signature of a two-way street. Options B and C each pick only one direction and overstate it as proof; a cohort study shows prediction over time, and hidden confounders can't be fully ruled out.

Concept Tested: Bidirectional Relationship **Bloom's Level:** Analyze

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Question 10

In The Two-Way Street MicroSim, setting gut to brain at 0.30 (with brain to gut at 0) and then switching to brain to gut at 0.30 (with gut to brain at 0) gives about the same snapshot correlation both times, but the "earlier, later" bars swap. What does this show?

A. Snapshot surveys are better than cohort studies for finding direction

B. The direction of an effect has no influence on any measurement

C. A single snapshot can't reveal the direction, but following people over time can help

D. A confounding variable must be present whenever two things are correlated

Show Answer

The correct answer is **C**. Opposite directions produce similar correlations at one moment, which is the reverse causation problem. The time-lagged correlations differ, which is why cohort studies help. Option D is wrong: in these settings there is no confounder at all, yet a correlation still appears.

Concept Tested: Reverse Causation **Bloom's Level:** Analyze

Chapter 12: Celiac Disease and Food Reactions

Summary

Celiac disease is a lifelong immune reaction to gluten that damages the tiny, finger-like villi lining the small intestine, and it affects about 1 in 100 people worldwide. This chapter explains why only people with certain gene variants get it, how a blood test and a small bowel biopsy confirm it, why the gluten-free diet is the only proven treatment, and how celiac disease can reach the nervous system. It then sorts out the confusing family of food reactions: food allergy, food intolerance (such as lactose intolerance), and non-celiac gluten sensitivity, where blinded trials suggest a carbohydrate called fructan may often be the real trigger. Along the way you will see why cutting out foods without a reason can backfire.

Concepts Covered

1. Celiac Disease
2. Gluten
3. HLA-DQ2 and HLA-DQ8
4. Intestinal Villi
5. Villous Atrophy
6. Tissue Transglutaminase Antibody
7. Small Bowel Biopsy
8. Gluten-Free Diet
9. Gluten Ataxia
10. Peripheral Neuropathy
11. Non-Celiac Gluten Sensitivity
12. Fructan
13. Food Allergy
14. Immunoglobulin E
15. Food Intolerance
16. Lactose Intolerance
17. Unneeded Restrictive Diet

Prerequisites

- Chapter 3: Meet the Microbiome (correlation vs causation)
- Chapter 4: The Immune System as a Sense Organ (gut immune cells and cytokines)
- Chapter 10: IBS and Disorders of Gut-Brain Interaction (FODMAPs and the placebo response)

Not every food reaction is the same reaction



Gluten-free labels are everywhere, and almost everyone knows someone who "can't eat" some food. Some of those reactions are serious immune diseases, some are digestion problems, and some are still a scientific puzzle. By the end of this chapter you'll be able to tell them apart, and you'll know why the order of testing matters so much.

12.1 The Gluten-Free Puzzle

Sam's older cousin, the one who keeps posting about supplements, has a new announcement. He has gone gluten-free, and he says his "brain fog" is gone. His post ends with a link to a gluten-free snack brand and the line "Gluten is poison for everyone's brain." Sam rolls his eyes, but he also wonders. Gluten-free menus are at every restaurant in town. Is gluten actually bad for everyone? (Sam, Riya, and their friends are fictional students who appear throughout this book.)

Meanwhile, Riya has a real reason to care about gluten. A girl in her orchestra section, Mei (also fictional), was diagnosed with celiac disease last year. When Riya and her grandmother bake for the orchestra potluck, Mei can't eat anything made with regular flour, and she can't even eat a gluten-free cookie if it was cut with the same knife as a regular one. For Mei, gluten is not a lifestyle choice. It is a trigger for an immune attack on her own intestine.

Here is the puzzle. A 2018 review of 96 studies estimated that about 1 in 100 people worldwide has celiac disease. Yet in a US national survey, the share of people who avoided gluten *without* having celiac disease more than tripled in just a few years, from 0.5% in 2009 to 2010 to 1.7% in 2013 to 2014, according to a 2016 analysis by Choung and colleagues. By then, more people were avoiding gluten without a diagnosis than had celiac disease at all (about 0.7% of people in the same survey). So who actually needs to avoid gluten, and why? To answer that, we need to look at the lining of the small intestine up close.

12.2 A Carpet That Feeds You: The Intestinal Villi

Picture two bath mats. One is a flat rubber mat. The other is a thick, shaggy towel-like mat with thousands of soft loops. Spill a glass of water on each. The flat mat barely holds any; the shaggy one soaks it up, because all those loops add up to a huge surface. Your small intestine is built like the shaggy mat.

Intestinal villi are tiny, finger-like projections of the small intestine's lining that greatly increase its surface area for absorbing nutrients. According to the open textbook *Anatomy and Physiology 2e* from OpenStax, each villus is only about 0.5 to 1 millimeter long, and there are about 20 to 40 of them in every square millimeter of lining. Inside each villus is a tiny bed of blood capillaries and a lymph vessel, which carry absorbed nutrients away.

The surface gets even bigger at a smaller scale. Each absorbing cell on a villus is covered with **microvilli**, hair-like extensions of the cell membrane about 1 micrometer long. Under a microscope, they look like the bristles of a brush, so together they are called the brush border. Enzymes stuck to the brush border finish digesting carbohydrates and proteins. One of those enzymes, lactase, breaks down the milk sugar lactose, which will matter in Section 12.9.

OpenStax notes that the folds of the lining, the villi, and the microvilli together increase the small intestine's absorptive surface more than 600-fold compared with a smooth tube. That is the whole point: food is broken into small molecules, and those molecules must touch a cell to get into your body. More surface means more absorption.

Level	Structure	Rough size	What it adds
Biggest	Circular folds of the lining	Ridges you can see with the naked eye	Slow food down and add surface
Middle	Villi	About 0.5 to 1 mm long	Tens of villi per square millimeter
Smallest	Microvilli (brush border)	About 1 micrometer	Huge membrane surface plus digestive enzymes

Now imagine someone mowing the shaggy mat down until it is nearly flat. The mat still exists, but it can't soak up much. That is what celiac disease does to the small intestine.

12.3 What Celiac Disease Is

Celiac disease is a lifelong, immune-driven disorder in which eating gluten triggers the immune system to damage the lining of the small intestine. The American College of Gastroenterology (ACG) 2023 guideline defines it as a permanent immune-mediated response to gluten. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) calls it a chronic digestive and immune disorder. Many scientists describe it as **autoimmune**, meaning the immune system attacks the body's own tissue, because the immune reaction damages the person's own intestine and produces antibodies against one of the body's own enzymes (more on that in Section 12.4).

Gluten is a group of proteins found naturally in wheat, barley, and rye. It gives bread dough its stretch. According to NIDDK, gluten is in obvious foods like bread, pasta, cookies, and cakes, but also in many

processed foods, because ingredients such as some starches, flavorings, and malt are made from these grains.

Who can get it: the gene "key"

This next fact surprises many people: celiac disease almost never develops unless a person carries certain gene variants. Think of it like a lock and key. The genes make a "display stand" on immune cells, and only some display stands hold gluten pieces in a way that sets off an alarm.

HLA-DQ2 and HLA-DQ8 are versions (variants) of immune-system genes in the human leukocyte antigen (HLA) family that make proteins on certain immune cells; nearly everyone with celiac disease carries one or both. MedlinePlus Genetics, a US National Library of Medicine site, explains that HLA proteins hold up small protein fragments so other immune cells can check whether they are "self" or "foreign." In celiac disease, the immune system wrongly treats fragments of gluten as a threat.

But carrying the key is not enough. NIDDK says about 30% of people have DQ2 or DQ8, yet only about 3% of those carriers develop celiac disease. A person also has to eat gluten, and other genes and environmental factors (such as early infections, which researchers are still studying) probably play a role. That means a genetic test is more useful for ruling celiac disease *out* than for ruling it *in*: if you don't carry DQ2 or DQ8, celiac disease is very unlikely.

How common is it?

Measure	Figure	Source
Worldwide, positive blood test	1.4% (in 275,818 people)	Singh et al. 2018 meta-analysis
Worldwide, confirmed by biopsy	0.7% (in 138,792 people)	Singh et al. 2018 meta-analysis
North America, confirmed by biopsy	0.5%	Singh et al. 2018
United States, estimated number of people	About 2 million	NIDDK

So "about 1 in 100 people worldwide" is a fair summary. Singh's review also found celiac disease more common in females than males (0.6% vs 0.4%) and in children than adults.

NIDDK notes that many people with celiac disease have not been diagnosed, that some people have celiac disease along with other immune-related conditions such as type 1 diabetes or thyroid disease, and that it is more common in people with certain chromosome conditions such as Down syndrome. It also runs in families: MedlinePlus Genetics says parents, siblings, and children of someone with celiac disease have about a 4 to 15% chance of developing it.

A gene that's necessary, not sufficient



I like to think of DQ2 and DQ8 as a ticket to a concert: almost nobody gets in without one, but holding a ticket doesn't mean you'll go. About 30% of people hold the ticket, and only about 3% of them ever get celiac disease.

12.4 Villous Atrophy: What the Damage Looks Like

What happens when someone with celiac disease eats gluten? The chain of events goes like this.

1. **Gluten arrives.** Gluten proteins are tough, and some fragments survive digestion and reach the lining of the small intestine.
2. **An enzyme changes the fragments.** An enzyme in the intestine called tissue transglutaminase (tTG) chemically modifies gluten fragments. A 2021 trial report by Schuppan and colleagues in the *New England Journal of Medicine* explains that this change makes the fragments stimulate immune T cells more strongly.
3. **The display stand shows them.** Immune cells carrying DQ2 or DQ8 hold up the modified fragments, and T cells (white blood cells that direct immune attacks) react as if they had found an invader.
4. **Inflammation follows.** The activated immune cells release inflammatory signals (cytokines, which you met in Chapter 4), and immune cells crowd into the lining.
5. **The villi shrink.** The lining is damaged faster than it can rebuild. The villi get shorter and blunter, and in severe cases flatten almost completely.
6. **The body makes antibodies against itself.** The immune system also makes antibodies against tTG, the body's own enzyme. That's part of why celiac disease is called autoimmune, and it is what the main blood test looks for.

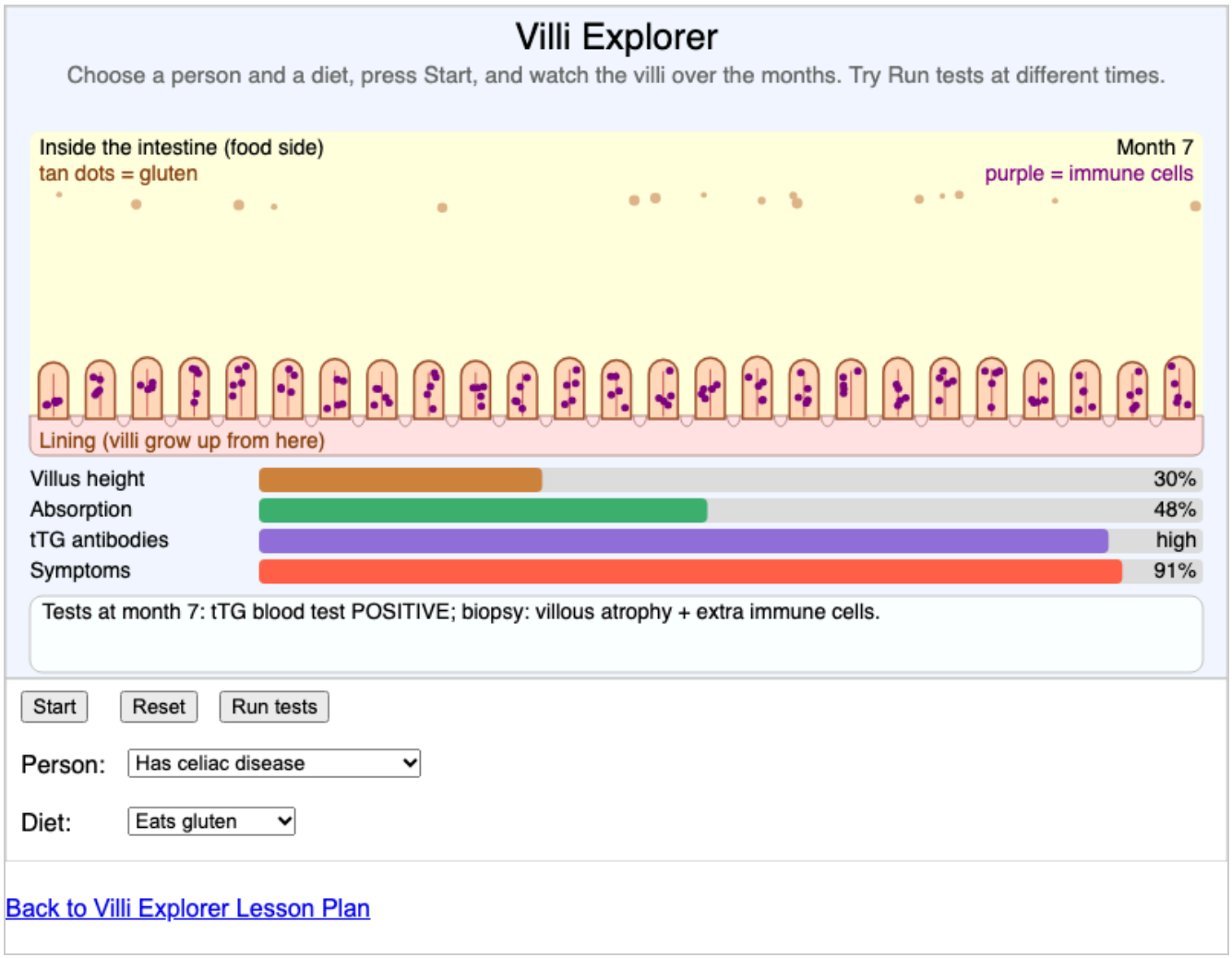
The result is **villous atrophy**, the shortening and flattening of the intestinal villi, seen under a microscope, that is the hallmark damage of celiac disease. MedlinePlus Genetics describes the villi in celiac disease becoming shortened and eventually flattening out. A 2018 *Lancet* review by Lebwohl, Sanders, and Green says the diagnosis requires villous atrophy in the first part of the small intestine (the duodenum).

With less surface, the intestine absorbs less. That one fact explains many celiac symptoms, which NIDDK lists as including diarrhea, bloating, gas, belly pain, and greasy stools; in children, slow growth, weight loss, delayed puberty, and damage to tooth enamel; and in anyone, fatigue, anemia (low red blood cells, often from poor iron absorption), and weak bones. Damage to the brush border can also reduce lactase, so NIDDK notes that some people with celiac disease become lactose intolerant until the lining heals.

Symptoms vary a lot. NIDDK says digestive symptoms are more common in children than adults, and some people have no obvious symptoms but still have damage. MedlinePlus Genetics notes that, on average,

diagnosis comes 6 to 10 years after symptoms begin, partly because tiredness and belly pain have many other causes.

Diagram: Villi Explorer



Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch12-villi-explorer/main.html

Open the Villi Explorer fullscreen

MicroSim specification: Villi Explorer

Type: microsim **sim-id:** ch12-villi-explorer
Library: p5.js
Status: Implemented
Bloom Level: Understand
Bloom Verb: explain
Learning Objective: The learner will explain how gluten exposure in celiac disease shortens the intestinal villi and reduces absorption, why the villi stay normal in a person without celiac disease, and why testing must happen before a gluten-free diet starts.

Canvas: 440 px drawing area plus 120 px controls (iframe 562 px); responsive to about 380 px wide.

Controls: Start/Pause, Reset, Run tests; Person select (Has celiac disease; Does not have celiac disease); Diet select (Eats gluten; Gluten-free diet).

Rules: Time advances in months. With celiac disease and gluten, inflammation and tTG antibodies rise over weeks and villus height falls toward a flat lining over a few months. On a gluten-free diet, symptoms and inflammation settle within weeks, antibodies fall over months, and villi regrow slowly (many months to years). Without celiac disease, villi stay normal on either diet. Run tests reports a tTG blood test (positive above a set level) and a biopsy result (villous atrophy when villi are clearly shortened).

Feedback: Meters show villus height, absorption, tTG antibody level, and symptoms; a status panel explains the current state and the last test result.

Provenance: Sections 12.2 to 12.6 (OpenStax A&P 2e; NIDDK; Lebwohl 2018; Rubio-Tapia 2010 for slow mucosal recovery). All rates and percentages are illustrative.

Start with **Has celiac disease** and **Eats gluten**, then press Start. Over the first few simulated months, purple immune cells crowd into the lining, the villi shrink, and the absorption meter drops. Press **Run tests** once the villi look short: the blood test and biopsy both come back positive. Now switch the diet to **Gluten-free diet** and keep watching. The symptom meter falls fast, but the villi take much longer to grow back, and the antibody meter falls slowly.

Now try the key experiment. Press Reset, let the villi shrink again, then switch to gluten-free *before* running the tests. Wait about a year and a half of simulated time and press **Run tests**. The tests may now come back negative, even though the person still has celiac disease. Finally, choose **Does not have celiac disease** and run either diet: the villi stay tall no matter what.

What this model leaves out

- Real villous damage is patchy and graded by pathologists on scales with several levels; the sim shows one smooth "height."
- The timing is illustrative. Real people vary a lot: NIDDK says symptoms often improve within days to weeks, while healing of the lining can take months to years, and in one study of adults only about two thirds had confirmed healing by 5 years.
- The sim leaves out the genes (DQ2 and DQ8), the many immune cell types, and the tTG chemistry; "has celiac disease" stands in for all of it.
- Real gluten exposure is rarely all or nothing. Small amounts from cross-contact can keep damage going.
- The "absorption" and "symptom" meters are teaching cartoons, not measurements, and symptoms don't always match the amount of damage.

12.5 Testing: The Blood Test and the Biopsy

Because celiac symptoms overlap with IBS, lactose intolerance, and many other conditions, NIDDK says doctors don't diagnose celiac disease from symptoms alone. They use two main tests.

Tissue transglutaminase antibody (tTG antibody) testing is a blood test that measures antibodies against tTG, the body's own intestinal enzyme; high levels suggest active celiac disease. The ACG 2023 guideline says tTG antibody testing is very helpful for the first screening of people suspected of having celiac disease. The standard tTG test measures antibodies of a type called IgA. NIDDK notes that selective IgA deficiency, in which the body makes little or no IgA, is more common in people with celiac disease, so doctors may check a person's overall IgA level along with the tTG test.

A **small bowel biopsy** is the removal of tiny pieces of tissue from the small intestine, usually the duodenum, during an upper endoscopy, so a pathologist can look for villous atrophy and immune cells under a microscope. In an upper endoscopy, a doctor passes a thin, flexible tube with a camera through the mouth and stomach into the first part of the small intestine, according to NIDDK. The ACG guideline says a biopsy is required to confirm the diagnosis in most patients, although a no-biopsy route can be used for selected children who meet strict criteria.

Under the 2020 European pediatric guidelines (ESPGHAN), this route can be used in children whose tTG antibody level is at least 10 times the upper limit of normal, confirmed by a second antibody test (endomysial antibodies) on a separate blood sample; symptoms are no longer required.

Why "go gluten-free first" is a trap

Both tests look for the immune system's response to gluten. Take the gluten away, and the response fades: antibodies drop and the villi start to heal. That's great for treatment, but terrible for diagnosis. NIDDK states

plainly that doctors don't recommend starting a gluten-free diet before diagnostic testing, because the diet can affect test results.

Think of a smoke detector test. If you want to know whether the detector works, you have to make smoke while you test it. If you clear the room first, the detector stays silent, and you learn nothing about whether there was ever a fire.

Someone who has already gone gluten-free and wants to be tested should talk with their doctor about what to do. Reintroducing gluten for testing is a medical decision, so it should be planned with the care team, not done alone.

Test first, then change the diet



The most common mistake I see is someone cutting out gluten "just to see," feeling a bit better, and then getting a negative test months later. If you think gluten bothers you, the first step is a conversation with a doctor while you're still eating your usual diet.

12.6 The Gluten-Free Diet: Simple to Say, Hard to Do

The **gluten-free diet** is an eating plan that strictly avoids wheat, barley, rye, and ingredients made from them; for people with celiac disease it is lifelong and is the only proven treatment. The ACG 2023 guideline says treatment requires strict adherence to a gluten-free diet and lifelong medical follow-up, and that most patients respond very well. NIDDK says that for most people the diet heals the small intestine and prevents further damage, and many people notice symptoms improve within days to weeks.

"Strict" really means strict. NIDDK describes several challenges:

- **Hidden gluten.** Many additives, such as malt flavoring and some modified food starches, can come from gluten grains.
- **Cross-contact.** A gluten-free food can pick up gluten from a shared toaster, cutting board, fryer oil, or knife, like Mei's cookie in Section 12.1.
- **Labels.** In the United States, the FDA requires foods labeled "gluten-free" to contain less than 20 parts per million of gluten, an amount NIDDK says is too small to cause problems for most people with celiac disease.
- **Oats.** NIDDK says research suggests most people with celiac disease can safely eat moderate amounts of oats, but oats are often contaminated with other grains, so this is a question for a doctor or dietitian.
- **Cost.** NIDDK notes that packaged gluten-free foods tend to cost more than the regular versions.

That's why NIDDK recommends a registered dietitian, a nutrition professional who can teach label reading, plan balanced meals, and check for nutrient gaps. Many foods are naturally gluten-free, including rice, potatoes, corn, beans, fruits, vegetables, meat, and fish, so the diet doesn't have to be bland. Riya's

grandmother, who cooks a lot of rice and lentil dishes, discovers that many family recipes were gluten-free all along; the things to watch are spices or mixes that may contain wheat, and utensils that need to stay separate.

Follow-up matters too. NIDDK says doctors may recheck antibody levels, which typically return to normal on the diet, and sometimes repeat a biopsy. About 20% of people with celiac disease have symptoms that continue or return on a gluten-free diet, according to NIDDK. Causes include small amounts of hidden gluten and other health problems. A rare form called refractory celiac disease doesn't heal even on a strict diet and needs specialist care.

Healing is slower than feeling better. In a 2010 Mayo Clinic study of 241 adults with biopsy-proven celiac disease, Rubio-Tapia and colleagues found confirmed healing of the lining in about 34% by 2 years and about 66% by 5 years, and feeling better did not reliably predict whether the lining had healed.

If you're going through this

If you've just been diagnosed with celiac disease, it's normal to feel overwhelmed, or even to grieve foods you love. You're not being dramatic; food is tied to family, culture, and friendship. A dietitian can help you find safe versions of your favorite meals, and many teens find it easier once they have a few go-to snacks and a short script, like "I have celiac disease, so I can't share, but thanks." If you keep having symptoms on the diet, tell your care team instead of assuming you failed. Hidden gluten is common and fixable.

12.7 Beyond the Gut: Celiac Disease and the Nervous System

Celiac disease is not only a gut disease. The ACG guideline describes it as resembling a multisystem disorder. NIDDK lists nervous system symptoms such as headaches, balance problems, seizures, and peripheral neuropathy, as well as mental health problems such as depression or anxiety.

Peripheral neuropathy is damage to the peripheral nerves (the nerves outside the brain and spinal cord), often causing numbness, tingling, burning, or weakness, usually starting in the hands and feet. You can picture it like a frayed phone cord: messages from the skin arrive garbled or not at all.

Gluten ataxia is a problem with balance and coordination linked to gluten sensitivity, thought to involve immune damage to the cerebellum, the part of the brain that fine-tunes movement. (For a refresher on the cerebellum, see From Neuron to Bedside, Chapter 7.) "Ataxia" means unsteady, uncoordinated movement.

How common are these? A 2019 systematic review by Mearns and colleagues pooled 16 studies of people with celiac disease. Neuropathy was reported in **up to** 39% of patients across 13 studies, while gluten ataxia was much less common, from 0% to 6% across 9 studies. The numbers vary widely because the studies were small and used different methods, so "up to 39%" is the top of a wide range, not a typical rate. The review also found that sticking to a gluten-free diet appeared to improve both conditions. Note that several authors of that review worked for or consulted for a drug company (Takeda), which the paper discloses.

Neurological problems in people with celiac disease have been reported since 1966, according to a 2010 *Lancet Neurology* review by Hadjivassiliou and colleagues, but exactly how a gluten-triggered immune reaction leads to nerve damage is still being studied.

What about mood? A 2012 meta-analysis by Smith and Gerdes of 18 depression studies found that depression was more common or more severe in adults with celiac disease than in healthy adults, but about the same as in adults with other long-term physical illnesses. Anxiety was not reliably different. That pattern suggests the link may come partly from the general stress of living with a chronic illness, not from something unique to gluten. It's a correlation, so it can't tell us the cause.

Hype Meter: "Celiac disease can affect your nerves and brain, not just your gut"

Strong	**Moderate**	Preliminary	Hype

Verdict: Moderate. Human studies consistently link celiac disease with peripheral neuropathy (reported in up to 39% of patients across small studies) and, less often, gluten ataxia (0% to 6%), and NIDDK lists nervous system symptoms as part of the disease. But the studies are small and varied, the exact mechanism is unclear, and the evidence that the gluten-free diet helps comes from observation, not randomized trials. **What would change the grade:** Large studies that follow people from diagnosis with careful nerve testing, plus a clear mechanism, could move it to Strong.

"Gluten is poison for everyone's brain"

Sam's cousin made a much bigger claim: that gluten harms *everyone's* brain. Popular books and posts have spread this idea, often by stretching what is true for people with celiac disease to the whole population.

Hype Meter: "Gluten damages everyone's brain"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. The best available test in people without celiac disease, a 2021 study of 13,494 US women, found no difference in memory and thinking scores between women who ate the most gluten and those who ate the least, over decades of diet records. The authors concluded their results do not support cutting gluten to protect thinking in people without celiac disease or established gluten sensitivity. Nervous system problems are a real concern for people *with* celiac disease, not proof of harm for everyone. **What would change the grade:** Repeated randomized trials showing that people without celiac disease think better after cutting gluten than after a disguised placebo diet. No such evidence exists.

Here is a closer look at that 2021 study by Wang, Lebwohl, and colleagues. It used the Nurses' Health Study II: women filled out food questionnaires from 1991 to 2015, then took computer-based tests of attention,

memory, and overall thinking between 2014 and 2019. After adjusting for other factors, gluten intake was not linked to any of the three scores.

How to read a gut-brain claim: gluten and thinking in 13,494 women

Question	This study
Mouse or human?	Human: 13,494 US women without celiac disease, average age about 61.
Correlation or cause?	Correlation (an observational cohort). It found *no* link, which is good evidence against a large harm, but it can't prove zero effect.
How many?	Large: 13,494 women. All were women, mostly middle-aged, so results may not apply to teens or men.
How long?	Diet tracked from 1991 to 2015 (about 24 years); thinking tested once, from 2014 to 2019.
Who paid for it?	US National Institutes of Health grants, plus foundation and research awards to some authors; the paper says funders had no role in the study's design or conclusions.
Is something being sold?	No product. Some authors reported personal fees from drug or nutrition companies for work outside this study, as disclosed in the paper.

The careful conclusion: for people without celiac disease, there's no good evidence that eating gluten harms thinking, and decent evidence against a big effect. It doesn't prove nobody is sensitive to wheat, which is the next question.

12.8 Non-Celiac Gluten Sensitivity and the Fructan Twist

Some people without celiac disease or wheat allergy say they feel better when they stop eating wheat. Their symptoms, often bloating, belly pain, tiredness, or "fog," are real. The question is what causes them.

Non-celiac gluten sensitivity (NCGS) is a condition in which people without celiac disease or wheat allergy report gut or other symptoms after eating gluten-containing foods that improve when they avoid them; unlike celiac disease, it doesn't damage the villi, and it has no biomarker. NIDDK notes that gluten sensitivity does not damage the small intestine. Because there is no blood test for NCGS, a 2015 group of experts (the Salerno criteria, Catassi and colleagues) proposed a standard test: a double-blind, placebo-controlled gluten

challenge. In plain words, the person eats food that secretly contains gluten for a week and food that doesn't for another week, and neither the person nor the researchers know which is which until the end.

When scientists run blinded tests like this, something surprising often happens.

- In a 2013 study by Biesiekierski and colleagues, 37 adults with self-reported gluten sensitivity and IBS first ate a diet low in FODMAPs (fermentable carbohydrates you met in Chapter 10). Their symptoms improved. Then, when they were secretly given gluten or a placebo protein, symptoms got worse by similar amounts with both. Gluten-specific effects showed up in only 8% of participants.
- In a 2017 meta-analysis of 11 gluten rechallenge studies, Lionetti and colleagues found that about 30% of people with suspected NCGS had symptoms return on gluten, but overall, relapse on gluten was not significantly different from relapse on placebo. In the studies that followed the stricter Salerno method, though, more people relapsed on gluten than on placebo (40% vs 24%), so a small group may truly react to gluten.
- In a 2018 study by Skodje and colleagues in Norway, 59 people on a self-chosen gluten-free diet (with celiac disease ruled out) ate muesli bars containing gluten, fructan, or neither, for a week each, in random order, without knowing which. Symptom scores were highest with fructan, and gluten was no different from placebo.

That last study introduces a new player. A **fructan** is a carbohydrate built from linked fructose (fruit sugar) units that the human small intestine can't break down; it is a type of FODMAP found in wheat and some other foods, and once it reaches the colon it can draw in water and increase gas, which can trigger symptoms in sensitive people. Wheat, barley, and rye contain both gluten (a protein) and fructans (carbohydrates). So when someone stops eating wheat and feels better, they've cut both at once, and the gluten-free label gets the credit.

There's also the placebo and nocebo side. When people expect a food to make them sick, they often feel worse after eating it, even when it is secretly a placebo. That is visible in these trials, where symptoms rose with the dummy food too. This doesn't mean the symptoms are "fake." Expectation changes how the brain processes gut signals, a real gut-brain effect you studied in Chapter 10.

Hype Meter: "Many people who think they're gluten sensitive are really reacting to fructans"

Strong	Moderate	**Preliminary**	Hype

Verdict: Preliminary. Blinded studies point away from gluten for many people: in one double-blind crossover trial of 59 adults, symptom scores were highest with fructan (clearly higher than with gluten), while gluten matched placebo, and an earlier trial of 37 adults found gluten-specific effects in only 8%. But these are small, short studies of adults, results differ between trials, and other wheat components may matter for some people. **What would change the grade:** Larger blinded trials in several countries, including teens, that test gluten, fructans, and other wheat parts separately and find the same pattern would raise it to Moderate.

The honest summary: NCGS is debated, not disproven. The symptoms are real; the trigger is uncertain, and for many people it may not be gluten. Because celiac disease must be ruled out first, and because diet changes have costs, the right path for anyone who suspects a wheat problem starts with a doctor.

12.9 Allergy, Intolerance, and Everything in Between

People often use "allergy," "intolerance," and "sensitivity" as if they mean the same thing. They don't, and mixing them up can be dangerous in one direction and wasteful in the other.

Food allergy: the immune system's alarm

A **food allergy** is a harmful reaction caused by a specific immune response that happens reliably every time a person is exposed to a particular food. That definition comes from the 2010 US food allergy guidelines written by an expert panel sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). The guidelines say most food allergies are driven by a particular antibody, though some are not.

Immunoglobulin E (IgE) is a class of antibody that drives immediate allergic reactions; in food allergy, IgE made against a food protein sits on immune cells and triggers them to release chemicals within minutes when the food is eaten. Picture a smoke alarm wired directly to a sprinkler system: IgE is the hair-trigger sensor, and the immune cells it sits on (such as mast cells, which you met in earlier chapters) are the sprinklers. The NIAID guidelines describe upper gut symptoms of IgE food allergy appearing within minutes, and the most serious reaction, anaphylaxis, as a rapid, whole-body allergic reaction that can cause death. People with food allergies work with their doctors on an emergency plan.

A wheat allergy is a food allergy, and it is different from celiac disease. NIDDK explains that in both, the immune system reacts to wheat, but wheat allergy can cause symptoms like itchy eyes or trouble breathing and does not cause long-term damage to the small intestine. The NIAID guidelines describe celiac disease as an immune reaction to food that does *not* involve IgE.

Food intolerance: a processing problem

A **food intolerance** is a reliable, unpleasant reaction to a food that does not involve the immune system, often because the body can't fully digest something. The NIAID guidelines use exactly this distinction: reactions without an immune mechanism are intolerances, not allergies.

The classic example is **lactose intolerance**, digestive symptoms such as bloating, gas, and diarrhea after eating or drinking lactose (milk sugar), because the small intestine can't break down all of it. According to NIDDK, the problem underneath is lactose malabsorption: the small intestine makes low levels of lactase, the brush-border enzyme that breaks down lactose, and in many people lactase levels drop after infancy. Undigested lactose passes into the colon, where bacteria break it down and create fluid and gas.

NIDDK estimates that about 68% of the world's population has lactose malabsorption, and about 36% of people in the United States, though not everyone with malabsorption has symptoms. NIDDK says it is most

common in Africa and Asia and least common among people whose families come from Europe; in the United States it is more common among African American, American Indian, Asian American, and Hispanic or Latino people. Since most adults worldwide have it, lactose malabsorption is the *typical* adult human pattern, not a defect. Most people with lactose intolerance can handle some lactose.

NIDDK draws the contrast clearly: lactose intolerance is a digestion problem, while milk allergy is an immune system disorder. Someone with lactose intolerance who drinks a milkshake may have a miserable afternoon. Someone with a milk allergy could have a life-threatening reaction.

	Celiac disease	**Food allergy (IgE)**	**Lactose intolerance**	**Non-celiac gluten sensitivity**
Immune system involved?	Yes (T cells, tTG antibodies; not IgE)	Yes (IgE antibodies)	No	Unclear; no biomarker
Typical timing	Damage builds over weeks to years	Minutes to a few hours	Within a few hours of eating	Hours to days, varies
Intestine damaged?	Yes, villous atrophy	Not long-term (for IgE allergy)	No	No
Can be life-threatening right away?	No	Yes (anaphylaxis)	No	No
How it's diagnosed	tTG antibody blood test, small bowel biopsy	Allergy specialist testing and history	History, sometimes a hydrogen breath test	Ruling out other causes; blinded challenge in research
Trace amounts matter?	Yes, strictly	Often yes	Usually no; many tolerate some	Varies

Use the right word



Words matter here. Calling an intolerance an "allergy" at a restaurant is understandable. But when someone with celiac disease or a true allergy speaks up, staff need to know that trace amounts count. Being precise helps everyone get the right level of care.

12.10 When Avoiding Food Backfires

If gluten-free food is easy to buy, why not cut gluten (or dairy, or anything else) "just in case"? An **unneeded restrictive diet** is cutting out foods or whole food groups without a diagnosed medical reason, which can bring costs such as nutrient gaps, missed or delayed diagnoses, extra expense, and social stress, without a proven benefit. Here's what can go wrong:

- **A missed diagnosis.** As Section 12.5 explained, going gluten-free before testing can make celiac tests falsely negative. Someone who actually has celiac disease may never get a clear answer, and might later return to gluten without knowing their intestine is being damaged.
- **Nutrition gaps.** Whole food groups carry nutrients. NIDDK notes, for example, that people avoiding dairy need other sources of calcium and vitamin D. This is one reason NIDDK recommends that people with celiac disease work with a dietitian, and the same logic applies to anyone cutting out foods.
- **Cost and hassle.** NIDDK notes that packaged gluten-free foods tend to cost more.
- **Social stress and worry.** Constantly checking labels and avoiding shared meals can make eating feel stressful and isolating. For some people, focusing intensely on "bad" foods can turn into an unhealthy relationship with food. Food is not good or bad in a moral sense; it's a question of what a particular body needs.
- **Wrong conclusions.** As the NCGS trials showed, feeling better after cutting a food doesn't prove that food was the problem. Expectation, other changes made at the same time (like eating fewer FODMAPs or less processed food), and natural ups and downs in symptoms can all play a part.

None of this means food reactions are imaginary. It means the order matters: get checked first, while eating normally, and change your diet with professional help.

For families

If your teen has celiac disease, the biggest help is often practical: a gluten-free shelf, a separate toaster or cutting board, and relatives who understand that "just a little" isn't okay. Try not to describe foods as "good" or "bad," and avoid comments about weight; the goal is safety and health. If someone in the family wants to go gluten-free without a diagnosis, encourage a doctor visit first, because celiac disease runs in families and testing works best while still eating gluten. Ask the care team whether other relatives should be tested.

At the Bedside: Tired, Pale, and Not Growing

Meet the patient (fictional)

Lucía is 14 and in ninth grade. For about a year she has felt tired all the time, even after a full night of sleep, and she gets belly pain and bloating several times a week. Her parents notice she hasn't grown much since last year while her friends shot up. Her school nurse sees that she looks pale and suggests a checkup. Lucía figures she's just stressed about starting high school.

What the doctor checks: Her pediatrician reviews her growth chart (her height has fallen off her usual curve), asks about stools, diet, periods, and family history (no one in her family is known to have celiac disease, which doesn't rule it out, since many people with celiac disease are undiagnosed), and examines her belly and skin. Blood tests show iron-deficiency anemia. Because the symptoms could fit celiac disease, the doctor orders a tTG antibody blood test while Lucía is still eating her usual diet, and checks her total IgA level. Her tTG antibodies come back clearly high. She is referred to a pediatric gastroenterologist, who performs an upper endoscopy and takes a small bowel biopsy.

Connecting the signals: Fatigue plus iron-deficiency anemia plus slow growth points to poor absorption, not just poor eating. The pathologist sees shortened, flattened villi and extra immune cells in the lining. With fewer villi, Lucía's small intestine has much less surface to absorb iron and other nutrients, which explains the anemia, the tiredness, and the slowed growth.

Diagnosis: Celiac disease.

Why it happens: Lucía carries a DQ2 or DQ8 variant (most people with celiac disease do), and when she eats gluten, modified gluten fragments trigger T cells in her intestine. The resulting inflammation causes villous atrophy, the same process you watched in the Villi Explorer, and her immune system makes antibodies against tTG, which the blood test detected.

The mind-body side: At first Lucía is relieved to have an answer. Then the hard part starts: school lunches, sleepovers, and a family that bonds over home-cooked meals. She feels embarrassed asking friends to check ingredients, and anxious about getting sick at a party. Her care team names this social stress as part of the illness, not a side issue. A dietitian helps her plan safe options for school and events, the team screens her for anxiety and low mood at visits, and she joins a teen celiac support group online where other teens share practical tips. Her parents learn to set up the kitchen so she isn't the only one adjusting.

Treatment today: A strict, lifelong gluten-free diet, taught by a registered dietitian, is the only proven treatment. Her team checks for and treats nutrient shortfalls such as low iron, monitors her growth, and rechecks her antibody levels over time. They also suggest that her close relatives talk to their doctors about testing.

What's new in research: Scientists are testing medicines that might reduce damage from accidental gluten exposure. In a 2021 trial in the *New England Journal of Medicine*, Schuppan and colleagues gave 163 adults with well-controlled celiac disease either a placebo or an experimental pill (ZED1227) that blocks the tTG enzyme, while all of them ate a measured amount of gluten daily for 6 weeks. Biopsies showed less gluten-induced damage to the villi in the drug groups than in the placebo group. The trial was funded by the drug's developer. **Evidence grade: Preliminary.** It was a short, early trial in adults; the drug is experimental and is not

an approved treatment, and it was tested as an add-on to the diet, not a replacement. As of October 2026, no medicine is FDA approved to treat celiac disease, though several are being tested in trials.

Your turn: reason through a variation

Lucía's older brother, 17, has no symptoms, but after her diagnosis he decides to stop eating gluten "to be safe." Two months later, his doctor orders a tTG antibody test, and it is normal. Does this show he doesn't have celiac disease?

Answer: Not necessarily. tTG antibodies fall when gluten is removed, so a normal result after two months gluten-free could be a false negative. He might not have celiac disease, but the test can't tell well in this situation. His doctor might discuss options such as genetic testing for DQ2 and DQ8 (if negative, celiac disease is very unlikely) or a planned, supervised return to gluten before retesting. This is why testing should happen before a diet change.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Celiac disease is a type of food allergy.
Reality: Celiac disease is an immune disorder, but it doesn't involve IgE, the antibody behind classic food allergies, and it damages the villi over time instead of causing an immediate allergic reaction. Wheat allergy is a separate condition.

Myth: If you think gluten bothers you, going gluten-free first will help the doctor figure it out.
Reality: NIDDK says doctors don't recommend starting a gluten-free diet before testing, because removing gluten can make the blood test and biopsy look normal even in someone with celiac disease.

Myth: A gluten-free diet is healthier for everyone.
Reality: For people with celiac disease it's essential, but in people without celiac disease, a 2021 study of 13,494 women found no link between gluten intake and thinking scores. Cutting gluten without a reason can cost more, complicate diagnosis, and narrow the diet.

Myth: Lactose intolerance is a milk allergy.
Reality: Lactose intolerance is a digestion problem: the small intestine can't break down all the lactose. A milk allergy is an immune reaction to milk protein that can be dangerous. NIDDK estimates about 68% of the world's people have lactose malabsorption, so it's very common and usually not dangerous.

Myth: If the genetic test shows DQ2 or DQ8, you have celiac disease.
Reality: About 30% of people carry DQ2 or DQ8, and only about 3% of carriers develop celiac disease. A negative gene test helps rule celiac disease out; a positive one doesn't rule it in.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Gluten-free cured my brain fog. Gluten is inflammatory for EVERYONE, so ditch it today! Use my code for 20% off."

Grade: Hype. One person feeling better isn't evidence of cause: expectation, other diet changes, and natural ups and downs could explain it, and blinded trials of self-reported gluten sensitivity often find gluten no worse than placebo. In people without celiac disease, a study of 13,494 women found no link between gluten intake and thinking scores. And there's a discount code, so someone profits from the claim. A careful version: "Gluten triggers real immune damage in people with celiac disease, about 1 in 100 people. If you think gluten affects you, get tested before cutting it out."

2. Predict: Riya's orchestra friend Mei has celiac disease and has followed a strict gluten-free diet for a year. At the potluck, she eats a gluten-free brownie that was cut with the same knife as a regular brownie. Predict what might happen in her intestine, and why.

The knife could transfer a small amount of gluten (cross-contact). In someone with celiac disease, even small amounts can restart the immune reaction: tTG-modified gluten fragments activate T cells, inflammation increases, and repeated exposures can shorten the villi again. One small exposure may or may not cause noticeable symptoms, but NIDDK notes symptoms can return with small amounts of gluten, which is why separate utensils matter.

3. Explain: A 15-year-old with untreated celiac disease starts having more bloating and gas after drinking milk. Explain how celiac disease could cause this.

Lactase, the enzyme that digests lactose, is part of the brush border on the microvilli of the small intestine. In untreated celiac disease, villous atrophy damages the lining and its brush border, so less lactase is available. Undigested lactose reaches the colon, where bacteria ferment it, producing gas and bloating. NIDDK lists lactose intolerance due to intestinal damage as a celiac symptom, and it often improves as the lining heals.

4. Apply: Sam's friend Jordan (fictional) gets hives and a swollen lip within 10 minutes of eating a shrimp dish. Jordan's sister gets bloated and has diarrhea a few hours after eating ice cream. Classify each reaction and explain the difference.

Jordan's reaction fits a food allergy, most likely IgE-mediated: it happened within minutes and involved the skin and lips, which is how IgE-triggered immune cells release chemicals fast. That kind of reaction can become serious, so Jordan should see a doctor about it. The sister's reaction fits a food intolerance such as lactose intolerance: a digestion problem without an immune attack, appearing hours later with gut symptoms. Only a doctor can confirm either, but the timing and symptoms point in different directions.

5. Read the data. In the 2018 Skodje trial, 59 adults with self-reported gluten sensitivity (celiac disease ruled out) ate muesli bars containing gluten, fructan, or neither (placebo) for a week each, in random order, without knowing which. Symptoms were scored on a gut symptom scale where higher means worse. Here are the published results:

Challenge	Average overall symptom score	Number of people whose worst week was this one
Gluten	33.1	13
Fructan	38.6	24
Placebo	34.3	22

5. What does this data show, and what can't it show?

On average, symptoms were highest during the fructan week, and the gluten week was no worse than placebo (33.1 vs 34.3). The paper reports fructan as significantly worse than gluten; its gap over placebo (38.6 vs 34.3) was smaller. Notice that 22 people had their worst week on placebo, which shows how strongly expectation and day-to-day variation affect symptoms. The data can't show that *no one* reacts to gluten, since averages can hide a few true responders, and it can't be generalized to teens or other countries from 59 adults in Norway tested for one week per food. A useful follow-up would be a larger blinded trial, including teens, that repeats each challenge more than once per person to see whether individual reactions are consistent.

Exercises

Remember

1. Name the three grains that naturally contain gluten.

Answer

Wheat, barley, and rye.

1. What are the two main tests used to diagnose celiac disease?

Answer

A tissue transglutaminase (tTG) antibody blood test, and a small bowel biopsy taken during an upper endoscopy to look for villous atrophy.

Understand

1. Explain why villous atrophy leads to poor absorption of nutrients.

Answer

Villi and their microvilli give the small intestine a huge surface for absorbing nutrients. When the villi shrink and flatten, there is much less surface touching digested food, so less iron, vitamins, and other nutrients get absorbed. That can cause anemia, fatigue, and slow growth.

1. Explain the difference between a food allergy and a food intolerance, using one example of each.

Answer

A food allergy is a reproducible reaction caused by the immune system, often driven by IgE antibodies and appearing within minutes; a peanut or milk allergy is an example, and it can be life-threatening. A food intolerance doesn't involve the immune system; lactose intolerance, where the gut can't fully digest milk sugar, is an example, and it causes uncomfortable but not dangerous gut symptoms.

Apply

1. Use the Villi Explorer. With "Has celiac disease" and "Eats gluten," let the villi shrink, then switch to "Gluten-free diet." Record roughly how many simulated months it takes the symptom meter to drop below 20% and how long the villus height takes to return above 80%. What real-world idea does the difference illustrate, and why can't you use the sim's exact numbers for a real person?
2. A classmate says, "My mom is going to test me for celiac disease next month, so I'm going gluten-free now to get a head start." Using what you know about tTG antibodies and biopsies, write the advice you would give, and explain who they should talk to.

Analyze

1. Compare the 2021 Wang study (13,494 women, gluten and thinking) with Sam's cousin's personal story about brain fog. For each, answer at least three of the six claim questions. Which tells you more about whether gluten harms the brain of a typical person, and why?
2. Wheat contains both gluten and fructans. Analyze why a person who feels better after cutting wheat can't conclude that gluten was the cause, and explain how the Skodje trial's design separated the two.

Evaluate

1. A school is considering making its whole cafeteria gluten-free "to be healthier for everyone." Evaluate this plan using evidence from this chapter, considering students with celiac disease, students without it, cost, and nutrition. What would you recommend instead?
2. Evaluate the claim that non-celiac gluten sensitivity "isn't real." Use the blinded trials, the placebo results, and the Salerno criteria to argue for a more careful statement.

Create

1. Design a blinded experiment to test whether a group of teens who say dairy gives them stomachaches are reacting to lactose. Describe your groups, how you would hide which drink is which, what you would measure, and what result would support the lactose explanation.
2. Create a one-page "eating with celiac disease" guide for a school's cafeteria staff. Include what gluten is, what cross-contact means, the US "gluten-free" labeling rule, and two respectful phrases staff can use with students, without making any medical recommendations about individual diets.

Key Takeaways

- Intestinal villi and their microvilli give the small intestine an enormous absorbing surface. In celiac disease, the immune reaction to gluten causes villous atrophy, which reduces absorption and can cause anemia, fatigue, and slow growth.
- Celiac disease affects about 1 in 100 people worldwide (1.4% by blood test, 0.7% confirmed by biopsy) and about 2 million people in the US. It requires HLA-DQ2 or HLA-DQ8 gene variants plus gluten, but only about 3% of carriers develop it.
- Diagnosis uses a tTG antibody blood test and, for most people, a small bowel biopsy. Testing must happen before going gluten-free, because the diet can make tests falsely negative.
- A strict, lifelong gluten-free diet is the only proven treatment. Symptoms often improve in days to weeks, but the lining can take months to years to heal, so follow-up matters.
- Celiac disease can affect the nervous system, including peripheral neuropathy and, less often, gluten ataxia (Moderate evidence). The claim that gluten harms everyone's brain is Hype.
- Food allergy (often IgE-driven, fast, possibly dangerous), food intolerance (non-immune, like lactose intolerance), celiac disease, and non-celiac gluten sensitivity are different conditions. Blinded trials suggest fructans, not gluten, may trigger symptoms in many people with self-reported gluten sensitivity (Preliminary).
- An unneeded restrictive diet can delay diagnosis, leave nutrient gaps, cost more, and add stress. Get checked first, then change your diet with professional help.

You can sort a food reaction like a scientist!



You now know why celiac disease is an immune disease, not an allergy or a fad, and why the order of testing matters. Next, in Chapter 13, we'll look at autism, ADHD, and the gut, where separating a real difference from a confounder matters a great deal.

Quiz: Celiac Disease and Food Reactions

Test your understanding of Chapter 12. Choose the best answer, then click **Show Answer** to check.

Question 1

Which grains naturally contain gluten?

A. Rice, corn, and potatoes

B. Wheat, barley, and rye

C. Oats, quinoa, and buckwheat

D. Wheat, rice, and soy

Show Answer

The correct answer is **B**. Gluten is a group of proteins found naturally in wheat, barley, and rye. Rice, corn, potatoes, quinoa, and buckwheat are naturally gluten-free. Oats don't naturally contain gluten but are often contaminated with other grains, which is why option C is a tempting mistake.

Concept Tested: Gluten **Bloom's Level:** Remember

Question 2

What are intestinal villi?

A. Muscle rings that squeeze food through the small intestine

B. Glands in the stomach that make acid

C. Bacteria that live on the lining of the colon

D. Tiny finger-like projections of the small intestine's lining that increase its surface area for absorption

Show Answer

The correct answer is **D**. Villi are about 0.5 to 1 millimeter long, are covered in microvilli, and give the small intestine a huge surface for absorbing nutrients. Option A describes the gut's smooth muscle, which moves food but doesn't absorb it.

Concept Tested: Intestinal Villi **Bloom's Level:** Remember

Question 3

Which antibody drives immediate allergic reactions, such as those in many food allergies?

A. Immunoglobulin E (IgE)

B. Tissue transglutaminase

C. Lactase

D. Gluten

Show Answer

The correct answer is **A**. IgE is the class of antibody behind immediate allergic reactions; it sits on immune cells and triggers them to release chemicals within minutes. Tissue transglutaminase (option B) is a body enzyme, and antibodies *against* it are a marker of celiac disease, which doesn't involve IgE.

Concept Tested: Immunoglobulin E **Bloom's Level:** Remember

Question 4

Why does carrying the HLA-DQ2 or HLA-DQ8 gene variant NOT mean a person has celiac disease?

A. Because the gene test is usually wrong

B. Because only people over 40 can develop celiac disease

C. Because about 30% of people carry these variants, but only about 3% of carriers develop celiac disease

D. Because these variants cause wheat allergy instead

Show Answer

The correct answer is **C**. The variants are almost always needed for celiac disease (nearly everyone with it has one), but they are not sufficient: about 30% of people carry them and only about 3% of carriers develop the disease. That's why a negative gene test helps rule celiac disease out, but a positive one can't rule it in. Option A is wrong because the test reliably detects the variants; the issue is what they mean.

Concept Tested: HLA-DQ2 and HLA-DQ8 **Bloom's Level:** Understand

---

Question 5

Why does villous atrophy in celiac disease often lead to anemia and fatigue?

A. Because gluten directly destroys red blood cells

B. Because flattened villi give less surface for absorbing nutrients such as iron

C. Because the villi make red blood cells

D. Because the gluten-free diet lacks iron

Show Answer

The correct answer is **B**. When the villi shrink and flatten, the small intestine has much less surface touching digested food, so it absorbs less iron and other nutrients, which can cause iron-deficiency anemia and tiredness. Option D reverses cause and effect: the anemia comes from the untreated disease, and a well-planned gluten-free diet helps the lining heal.

Concept Tested: Villous Atrophy **Bloom's Level:** Understand

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Question 6

What is the key difference between lactose intolerance and a milk allergy?

A. Lactose intolerance is a digestion problem without an immune attack, while a milk allergy is an immune reaction to milk protein.

B. Lactose intolerance is an immune reaction, while a milk allergy is a digestion problem.

C. They are the same condition with different names.

D. Lactose intolerance damages the villi, while milk allergy does not.

Show Answer

The correct answer is **A**. In lactose intolerance, the small intestine makes too little lactase to digest all the milk sugar, and colon bacteria break down the rest, causing gas and bloating. A milk allergy is an immune system disorder that can be dangerous. Option B swaps the two, which is the most common confusion.

Concept Tested: Lactose Intolerance **Bloom's Level:** Understand

---

Question 7

Dev, 16 (fictional), has had belly pain and tiredness for months. His appointment for celiac testing is in three weeks, and he plans to stop eating gluten today "to get a head start." What is the best response, based on this chapter?

A. Good idea, because a gluten-free diet makes the tests more accurate.

B. Good idea, because if he feels better, he won't need the tests.

C. It doesn't matter, because celiac tests don't depend on what he eats.

D. He should talk to his doctor first, because going gluten-free before testing can make the tests look falsely normal.

Show Answer

The correct answer is **D**. Both the tTG antibody test and the biopsy detect the immune response to gluten, and removing gluten lets that response fade. NIDDK says doctors don't recommend starting a gluten-free diet before testing. Option B is a trap: feeling better on the diet doesn't show what caused the symptoms.

Concept Tested: Tissue Transglutaminase Antibody **Bloom's Level:** Apply

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Question 8

Within 10 minutes of eating a peanut cookie, Aaliyah (fictional) gets hives and her lips swell. Which condition does this pattern fit best?

A. Celiac disease

B. Lactose intolerance

C. A food allergy, likely driven by IgE

D. Non-celiac gluten sensitivity

Show Answer

The correct answer is **C**. A fast reaction (within minutes) involving the skin and lips fits an IgE-mediated food allergy, in which IgE on immune cells triggers a rapid chemical release. This kind of reaction can become serious and needs a doctor's evaluation. Celiac disease (option A) involves the immune system too, but it doesn't use IgE and its damage builds over weeks to years.

Concept Tested: Food Allergy **Bloom's Level:** Apply

Question 9

In the 2018 Skodje trial, adults with self-reported gluten sensitivity secretly ate gluten, fructan, or placebo for a week each. Average symptom scores were 33.1 (gluten), 38.6 (fructan), and 34.3 (placebo). What is the best conclusion?

A. In this group, fructan raised symptoms more than gluten, and gluten was no worse than placebo.

B. Gluten caused the most symptoms, proving gluten sensitivity is common.

C. The participants have undiagnosed celiac disease.

D. Placebo caused more symptoms than fructan.

Show Answer

The correct answer is **A**. Fructan produced the highest average score, and gluten (33.1) was about the same as placebo (34.3). That suggests fructans, a FODMAP in wheat, may be the trigger for many people who think they react to gluten, though one small, short study can't prove it for everyone. Option C is wrong because celiac disease had been ruled out before the study.

Concept Tested: Fructan **Bloom's Level:** Analyze

Question 10

A friend without celiac disease cut out gluten, dairy, and several other foods after reading a wellness post, and says, "It can't hurt." Which response best analyzes the risks of an unneeded restrictive diet?

A. There are no risks, because gluten-free foods are always healthier.

B. Restriction can delay or hide a real diagnosis, leave nutrient gaps, cost more, and add stress, so diet changes should start with a doctor.

C. The only risk is that it might be boring.

D. Restriction is risky only for people with celiac disease.

Show Answer

The correct answer is **B**. Cutting foods without a diagnosed reason can make celiac tests falsely negative, remove sources of nutrients like calcium and vitamin D, raise food costs, and make eating stressful. Option A is a common belief, but a large study of women without celiac disease found no benefit of low gluten intake for thinking scores.

Concept Tested: Unneeded Restrictive Diet **Bloom's Level:** Analyze

Chapter 13: Autism, ADHD, and the Gut

Summary

Autism and ADHD are neurodevelopmental differences: ways a brain develops and works, not diseases to fix. This chapter looks at what the gut-brain research actually shows. Autistic children have gut symptoms such as constipation and belly pain more often than other children, and those symptoms are real health problems worth treating. But headlines claiming that gut bacteria *cause* autism have not held up: a large 2021 study found that differences in diet, often linked to selective eating, explained most of the microbiome differences. You'll learn how confounders, open-label trials, placebo controls, and sample size shape what a study can prove, and why "cure" claims about autism and ADHD are both unsupported and harmful.

Concepts Covered

1. Autism
2. ADHD
3. Neurodiversity
4. Identity-First Language
5. GI Symptoms in Autism
6. Selective Eating
7. Interoceptive Differences
8. Diet as Confounder
9. Maternal Immune Activation
10. Open-Label Trial
11. Placebo-Controlled Trial
12. Sample Size
13. Microbiota Transfer Therapy
14. Harmful Cure Claims

Prerequisites

- Chapter 3: Meet the Microbiome (microbial diversity, correlation vs causation)
- Chapter 10: IBS and Disorders of Gut-Brain Interaction (the placebo response)

- Chapter 11: Anxiety, Depression, and the Gut (confounding variables)

A chapter about real people, so let's be careful



Some of you reading this are autistic or have ADHD, and some of you love someone who is. This chapter is about a real health issue (gut problems are common and treatable) and about a lot of overblown headlines. My goal is to help you sort the two, with respect for the people the research is about.

13.1 A Headline, and a Boy Named Leo

A few years ago, you could find headlines suggesting that gut bacteria might "cause" autism, and posts promising that changing the microbiome could "reverse" it. Then, in 2021, a team in Australia published a large, careful study in the journal *Cell* with a much less dramatic conclusion: the microbiome differences they found seemed to be explained mostly by differences in what children ate, not by autism itself.

Meet Leo. Leo is 12, autistic, and the kind of person who can tell you every stop on three different subway lines. (Leo is a fictional character, like everyone in this book's cases.) For months, Leo has been having a hard time: he wakes up at night, he's more irritable after school, and he has started pressing his stomach against the edge of the kitchen table. Leo talks, but describing what's going on inside his body is hard for him. His parents eventually figure out, with his doctor's help, that Leo has been badly constipated. Treating it doesn't change who Leo is. It just means his stomach stops hurting.

Sam has a connection to this topic too. His younger cousin Nico, who is 10, has ADHD. Sam's older cousin, the one who posts about supplements, recently shared a video claiming that ADHD is "caused by sugar and a toxic gut." Sam isn't buying it, but he wants to know what the evidence actually says. So do we.

13.2 Autism, ADHD, and Neurodiversity

Before we can talk about the gut, we need to be clear about what autism and ADHD are, and what they aren't.

Autism is a lifelong neurodevelopmental difference that affects how a person communicates and interacts with others, processes sensory information, and experiences the world, often including focused interests and repetitive behaviors. The National Institute of Mental Health (NIMH) describes autism as affecting how people interact, communicate, learn, and behave, with signs that generally appear in the first two years of life. It's called a "spectrum" because autistic people have a wide range of characteristics, needs, strengths, and challenges. NIMH lists strengths that many autistic people have, such as learning things in detail, remembering information for long periods, and excelling in areas like math, science, music, or art. Some autistic people need a lot of daily support; others need little.

How many people are autistic? According to the Centers for Disease Control and Prevention (CDC) Autism and Developmental Disabilities Monitoring Network, about 1 in 31 eight-year-olds (32.2 per 1,000) had been

identified as autistic in 2022, across 16 US sites, in a report published in 2025. Autism was identified about 3.4 times as often in boys as in girls. The estimate was higher than in earlier years, and the report points to increased identification, especially among very young children and groups that were previously under-identified.

ADHD (attention-deficit/hyperactivity disorder) is a neurodevelopmental condition involving ongoing patterns of inattention, hyperactivity, and/or impulsivity that show up in more than one setting and affect daily life. NIMH describes the three patterns: trouble staying focused and organized; moving, fidgeting, or talking a lot; and acting quickly without pausing. Everyone does these things sometimes. For a person with ADHD, they're frequent, start in childhood, and happen across settings like school and home. According to the CDC, about 7 million US children aged 3 to 17 (11.7%) had a current ADHD diagnosis in 2024, based on a national parent survey. NIMH says researchers aren't sure what causes ADHD, but many studies suggest genes play a large role.

What causes autism? NIMH says researchers don't know the primary causes, but studies suggest that genes and aspects of the environment before birth may affect development. Factors linked to a higher likelihood include having an autistic sibling, older parents, certain genetic conditions, and very low birth weight. None of these is a "cause" by itself, and gut bacteria are not on the list.

	Autism	**ADHD**
What it is	Neurodevelopmental difference in communication, social interaction, sensory processing, and patterns of interest and behavior	Neurodevelopmental condition involving inattention, hyperactivity, and/or impulsivity
When it starts	Signs usually appear in early childhood	Symptoms begin in childhood
How common (US)	About 1 in 31 eight-year-olds identified (2022)	About 11.7% of children aged 3 to 17 with a current diagnosis (2024)
Main known influences	Genes and early development (NIMH)	Genes play a large role (NIMH)
Caused by gut bacteria?	No evidence that it is	No evidence that it is

A different way to think about brains

Neurodiversity is the idea that natural variation in how human brains develop and work, including autism and ADHD, is part of normal human diversity, so the goal is understanding, support, and accommodation rather than cure. Think of it like handedness. Left-handed people were once forced to write with their right hands, as

if left-handedness were a defect. Today we see it as a difference that needs the right tools (left-handed scissors, a different desk), not a problem to fix.

The neurodiversity view doesn't mean autistic people or people with ADHD never struggle or never need help. Many face real challenges, and many have co-occurring health conditions, including gut problems, sleep problems, anxiety, and depression, that deserve good care. The key is to separate the *person and their way of thinking* from the *health problems* that can make their life harder. That separation is the whole spirit of this chapter.

Words matter: identity-first language

Identity-first language is a way of talking about a group that puts the identity first, such as "autistic person" instead of "person with autism," often preferred because many autistic people see autism as a core part of who they are rather than something they carry. This book uses identity-first language for autism by default.

Why? A 2021 commentary by Bottema-Beutel and colleagues in the journal *Autism in Adulthood*, drawing largely on writing by autistic scholars, describes how language can treat autism as something bad that should be fixed. They suggest neutral alternatives, such as "focused interests" instead of "special interests," and "increased likelihood of autism" instead of "at risk for autism," and they recommend avoiding talk of autism as a "burden."

People don't all agree, though. A 2016 UK survey of 3,470 people by Kenny and colleagues found that "autistic" was endorsed by many autistic adults and parents but by fewer professionals, and that no single term was preferred by everyone. The best rule: when talking about a specific person, use the words they prefer. You'll also notice this chapter avoids phrases like "suffers from autism" or "recovered from autism."

Two separate questions



Whenever you read about autism and the gut, I want you to split it into two questions. Question one: "Does this person have a gut problem that's hurting them?" Question two: "Does the gut cause autism?" The first is a health question with good answers. The second has a lot of hype attached.

13.3 Real Gut Problems, Worth Treating

One finding has held up well. **GI symptoms in autism** refers to the higher rate of digestive problems, such as constipation, diarrhea, and belly pain, reported in autistic children compared with non-autistic children; these are real health issues that deserve diagnosis and treatment, separate from autism itself.

The best summary comes from a 2014 meta-analysis (a study that pools results from many studies) by McElhanon and colleagues in the journal *Pediatrics*. They combined 15 studies that compared autistic children

with other children. Here's what they found, as odds ratios. (An odds ratio compares the odds of something in one group with the odds in another; 1.0 means no difference.)

Symptom	Odds ratio (autistic vs comparison children)
General GI symptoms	4.42
Constipation	3.86
Diarrhea	3.63
Abdominal pain	2.45

So autistic children had roughly four times the odds of general GI symptoms. That's a big difference. But notice what the authors were careful to say: the studies varied a lot in how they measured symptoms, and the analysis could not tell *why* the symptoms were more common. They named diet restrictions as one possible factor that future research should explore.

Hype Meter: "Autistic children have more gut symptoms on average"

Strong | Moderate | Preliminary | Hype

Verdict: Strong (as an association). A 2014 meta-analysis of 15 comparison studies found that autistic children had higher odds of general GI symptoms (about 4.4 times), constipation, diarrhea, and belly pain. The link is consistent across studies, though the size varies and the causes are not known. This grade is about the *association*; it does not mean the gut causes autism. **What would change the grade:** Very little would undo the association. Large studies with standard symptom measures would pin down how big it is and why it happens.

Why does this matter? Because these problems hurt. Constipation can cause belly pain, poor sleep, and a bad mood in anyone. When doctors and families recognize gut problems in autistic children, they can treat them with the same tools they use for other children. A 2010 set of expert recommendations in *Pediatrics*, led by Buie, concluded that autistic children with GI problems can benefit from adapting the standard pediatric guidelines for evaluating belly pain, chronic constipation, and reflux.

13.4 Why Gut Pain Can Be Hard to See

If autistic children have more gut problems, why do they sometimes go unnoticed for months, like Leo's? Two big reasons: how people sense their own bodies, and how they communicate about it.

Sensing the inside of the body

You have senses for the outside world (sight, hearing, touch) and also senses for the inside. That inner sense, called interoception, is how you notice hunger, fullness, a full bladder, a racing heart, or a stomachache. You learned in Chapter 2 that most vagus nerve fibers carry signals from the body up to the brain; interoception is what the brain makes of signals like those.

Interoceptive differences are differences in how a person notices, interprets, or reports signals from inside the body, such as hunger, pain, or the need to use the bathroom. A 2016 review by DuBois and colleagues found that interoception is atypical in autism on average, with a slight tendency toward *less* awareness of internal signals, but the direction and size of the difference vary a lot from person to person. Some autistic people may notice internal signals less; others may find them overwhelming.

Picture two smoke alarms. One is set to go off at the faintest wisp of smoke, and one only sounds when the kitchen is already full of it. Neither is "broken," but if you live with the second one, you need other ways to catch a small fire early.

Communicating about pain

Even when someone feels pain, putting it into words can be hard. Some autistic people speak fluently but find it hard to describe inner sensations on the spot. Some communicate using typing, picture boards, or speech-generating devices. Some show discomfort through behavior: sleep changes, irritability, pressing on the belly, or new repetitive movements. The 2010 Buie recommendations noted that autistic children with gut disorders may show their discomfort through changes in behavior.

That's why caregivers and doctors are encouraged to ask, when behavior changes suddenly, "Could something be hurting?" A change in behavior is information, not just a "behavior problem."

Selective eating

Many autistic people have strong food preferences. **Selective eating** is eating a limited range of foods, often because of sensitivity to taste, texture, smell, or appearance, or a strong need for sameness; it is more common in autistic children. A 2013 meta-analysis of 17 studies by Sharp and colleagues found that autistic children had about five times the odds of feeding problems compared with other children (odds ratio 5.11), and lower average intake of calcium and protein.

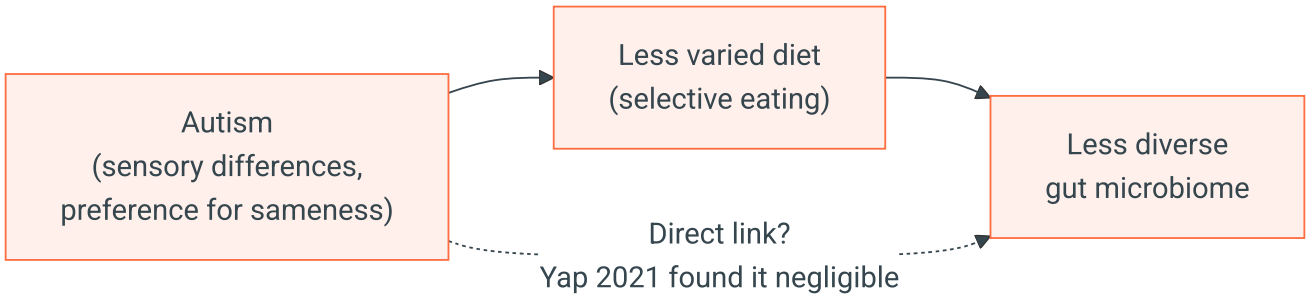
Selective eating isn't stubbornness. For someone with strong sensory responses, a new texture can feel truly unbearable, the way a fork scraping a plate feels to some people. But a narrow diet can sometimes mean less fiber, which can contribute to constipation, and it changes what gut bacteria get to eat. Hold on to that idea. It turns out to be the key to the next section.

13.5 The Microbiome Question: Diet as Confounder

Over the past two decades, many small studies reported that the gut microbiomes of autistic children looked different from those of non-autistic children. It was tempting to read an arrow from microbes to autism. But remember the rule from Chapter 3: correlation is not causation. And remember from Chapter 11 that a confounding variable is a third factor that affects both things you're measuring.

Here's an everyday example. Ice cream sales and sunburns rise together. Ice cream doesn't cause sunburns; summer weather drives both. Now apply that to the microbiome.

Diet as confounder is the idea that differences in what people eat can create an apparent link between a condition and the gut microbiome, because diet shapes the microbiome and may also differ between groups for reasons related to the condition. In autism research, if autistic children on average eat a narrower range of foods (selective eating), and diet shapes gut bacteria, then autistic children will have different gut bacteria on average, even if autism itself has no direct effect on the microbiome.



The 2021 study that changed the conversation

In 2021, Yap and colleagues published the study mentioned in this chapter's opening. They analyzed stool samples from 247 children and teens, from the Australian Autism Biobank and the Queensland Twin Adolescent Brain project, using metagenomics (reading all the microbial DNA in a sample). They also collected detailed information on diet, age, stool consistency, and other factors.

Their main findings:

- They found **negligible direct associations** between an autism diagnosis and the gut microbiome.
- Instead, the data fit a chain: autism-related restricted interests were linked to a **less diverse diet**, which was linked to **less diverse gut bacteria** and looser stools.
- Their study had enough data to detect microbiome links with things like age, diet, and stool consistency, so the missing autism link was not just because the study was too small.

The authors concluded that microbiome differences in autism may reflect dietary preferences, and they explicitly cautioned against claims that the microbiome drives autism.

A second look from another angle

Science moves forward by checking results in different ways. In 2023, Morton and colleagues pooled 10 microbiome data sets plus 15 other data sets (diet, metabolism, immune markers, brain gene activity) in

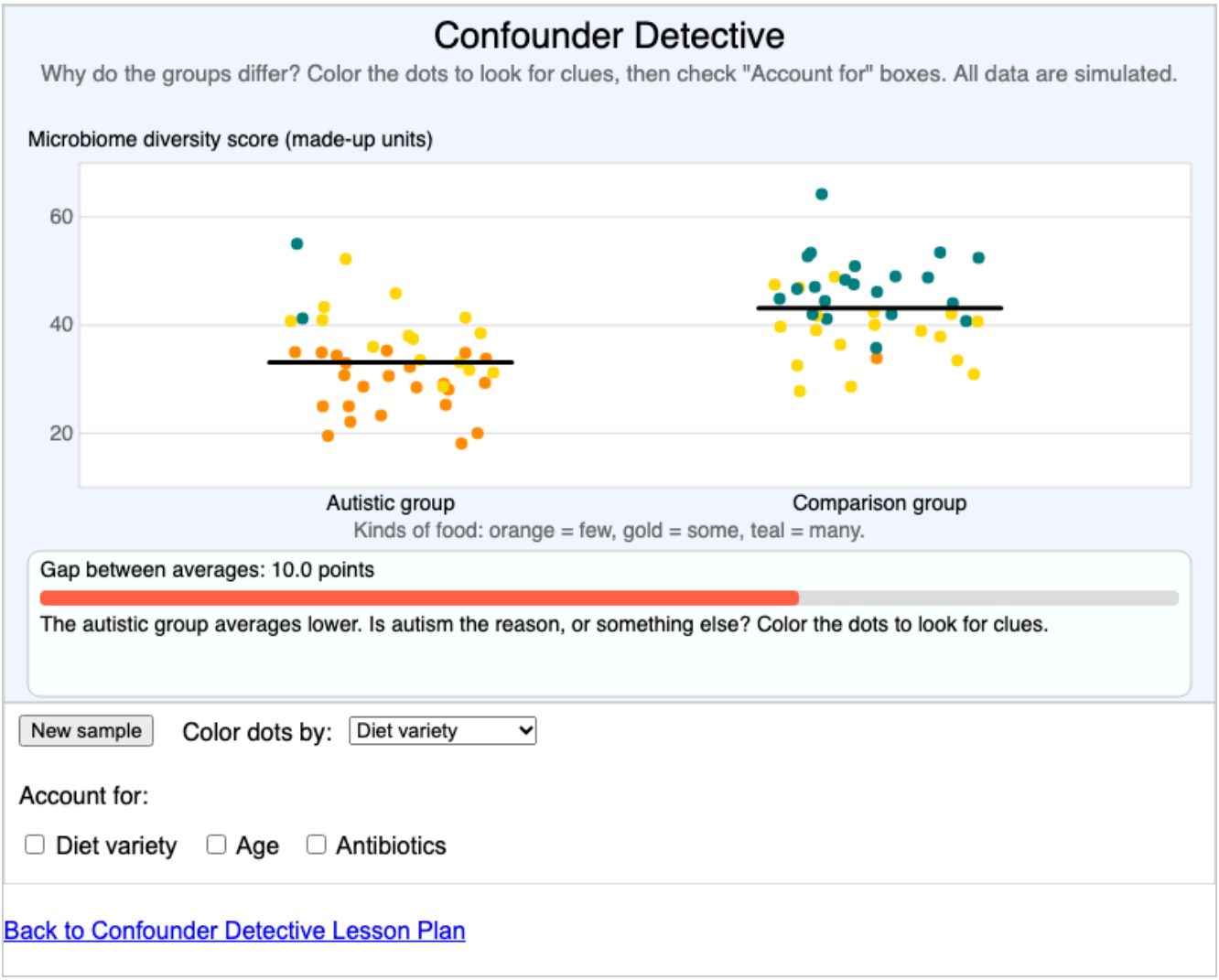
Nature Neuroscience. They did find autism-linked microbial and chemical patterns, and those patterns were associated with restrictive diets and inflammation markers. The key detail is that the pattern showed up when autistic children were compared with unrelated children matched by age and sex, and **did not** show up when autistic children were compared with their own siblings, who share their home, family meals, and much of their environment.

That's what you'd expect if shared environment and diet, not autism itself, explained much of the difference. Neither study shows that microbes cause autism. Together, they make diet a leading suspect for why the microbiomes differ.

The debate isn't over, though. In 2024, Su and colleagues in Hong Kong sequenced stool samples from 1,627 children aged 1 to 13 in *Nature Microbiology* and reported many microbial differences between autistic and non-autistic children, including in bacteria, fungi, and viruses. That study was larger than Yap's. But it was also observational: it took one snapshot of stool, so it can't show which came first or rule out every difference in diet and daily life. Bigger studies make a difference easier to detect. They don't, by themselves, show what caused it.

In the simulation below, you'll be the detective. Two groups of simulated children have different average microbiome diversity scores. Your job is to find out why.

Diagram: Confounder Detective



Back to Confounder Detective Lesson Plan

Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch13-confounder-detective/main.html

Open the Confounder Detective fullscreen

MicroSim specification: Confounder Detective

Type: microsim **sim-id:** ch13-confounder-detective
Library: p5.js
Status: Implemented
Bloom Level: Analyze
Bloom Verb: differentiate
Learning Objective: The learner will identify how a confounding variable (diet variety) can create an apparent difference in microbiome diversity between an autistic group and a comparison group, and distinguish a confounder from variables that are balanced between groups.

Canvas: 460 px drawing area plus 120 px controls (iframe 582 px); responsive to about 380 px wide.

Controls: New sample button; Color dots by select (None; Diet variety; Age; Recent antibiotics); Account for checkboxes (Diet variety; Age; Antibiotics).

Rules: 40 simulated children per group. Microbiome diversity depends on diet variety, age, and recent antibiotics, plus random noise. Group membership has no direct effect. The autistic group has lower average diet variety; age and antibiotic use are balanced between groups. Accounting for variables uses a linear regression and shows adjusted scores and the adjusted group difference.

Feedback: Group means, the raw and adjusted differences in points, and a status message explaining which variables changed the difference.

Provenance: Section 13.5 (Yap et al. 2021; Morton et al. 2023). All data are simulated; the model builds in "no direct effect" to teach confounding, not to report real effect sizes.

Start with **Color dots by: None** and look at the gap between the two groups' average lines. Now color the dots by **Age**, then by **Recent antibiotics**. Do the colors line up with the gap? Then color by **Diet variety**: you'll see that the low-diversity dots are mostly the children who eat fewer kinds of food, and there are more of those in the autistic group.

Next, check the **Account for** boxes one at a time. Accounting for age or antibiotics barely changes the gap, because those are spread evenly across both groups. Accounting for **Diet variety** shrinks the gap to nearly zero. Press **New sample** a few times: the leftover difference bounces around zero just from chance, which is a good reminder of why sample size matters.

What this model leaves out

- The data are simulated, and the model was built so autism has no direct effect. Real studies have to *discover* whether there's a direct effect, and they measure diet imperfectly.
- Real microbiomes have hundreds of species; a single "diversity score" hides most of that complexity.
- Real diets differ in many ways (fiber, variety, specific foods, food textures), not one number.
- The sim shows only three hidden variables. Real studies must consider many more, such as medications, sleep, stool consistency, and family environment.
- "Accounting for" a variable with a statistical model is useful but not perfect; it can't fix variables nobody measured.

13.6 What Mice Can and Can't Tell Us

Some of the strongest-sounding evidence for a gut-autism link comes from mice. Here's what it is, and why we keep it in its lane.

Maternal immune activation (MIA) is a strong immune response in a pregnant animal or person, such as from an infection; in research, it's usually triggered on purpose in pregnant mice to study how it affects the offspring's development. In mice, offspring of mothers given MIA show behaviors that researchers label "autism-like," such as differences in communication-related, repetitive, anxiety-like, and sensorimotor behaviors.

In a well-known 2013 study in *Cell*, Hsiao and colleagues found that MIA mouse offspring had leaky gut barriers and altered gut microbes. When the researchers gave these mice a human gut bacterium, *Bacteroides fragilis*, the gut barrier improved and some of the behaviors changed. They also found a microbe-linked chemical in the blood that, when given to normal mice, caused some behavior changes.

This is clever science, and it shows that in mice, gut microbes can affect behavior-related traits. But it is not evidence about autistic people, for several reasons:

- **A mouse "autism-like behavior" is not autism.** Autism is defined by human communication, social experience, sensory processing, and patterns of interest. Mice can model small pieces of biology, not a human identity.
- **The trigger was artificial.** The immune activation was caused on purpose in the lab, so it doesn't tell us whether anything similar happens in people.
- **Mouse results often don't carry over.** As Chapter 1 noted, many findings in mice are never confirmed in people.

Whether maternal immune activation plays any role in human autism is still an open research question. For this chapter, the takeaway is simple: mouse results are a reason to ask questions, not a reason to change how anyone treats an autistic child.

13.7 Reading Treatment Studies: Open Labels, Placebos, and Sample Size

Suppose someone claims a treatment helps. How do you judge it? Three parts of a study's design matter a lot.

An **open-label trial** is a study in which participants, families, and researchers all know who is getting the treatment; there's usually no placebo group, so improvements may come from expectations, extra attention, or time passing rather than the treatment. Think of tasting two sodas when you can see the labels. Your opinion is shaped by what you expect.

A **placebo-controlled trial** is a study that compares the real treatment with a look-alike dummy treatment (a placebo), ideally with assignment by chance and with neither participants nor researchers knowing who got which (double-blind), so that expectation effects are the same in both groups. You learned about the placebo response in Chapter 10. It's powerful, especially for outcomes rated by people who know what was given.

Sample size is the number of participants in a study; small samples give results that swing more by chance and can't detect uncommon side effects, so a finding in 18 people is a hint, while a finding in hundreds or thousands is much more reliable. Flip a coin 10 times and getting 7 heads isn't surprising. Flip it 1,000 times and getting 700 heads would be shocking. Bigger samples let chance even out.

The microbiota transfer therapy studies

Microbiota transfer therapy (MTT) is an experimental treatment protocol in which a person receives antibiotics, a bowel cleanse, and stomach-acid medicine, followed by repeated doses of processed stool from healthy donors (a fecal microbiota transplant) to try to replace their gut microbes. Fecal microbiota transplants are covered in more detail in Chapter 17.

In 2017, Kang and colleagues reported a small open-label trial of MTT in 18 autistic children aged 7 to 16 who all had moderate to severe GI problems. The protocol was long: 2 weeks of an antibiotic, a bowel-cleansing drink, a stomach-acid reducer, and then 7 to 8 weeks of daily donor-microbe doses. At the end of treatment, scores on a GI symptom scale were about 80% lower, with improvements in constipation, diarrhea, indigestion, and belly pain, and the improvement lasted at least 8 weeks. The researchers also reported changes on autism rating scales.

A 2019 follow-up of the same 18 children found that, two years later, GI symptom scores were still about 58% lower than at the start.

Those GI results are encouraging for the children's comfort and health. But look at what the design can and can't tell us.

How to read a gut-brain claim: the 2017 microbiota transfer therapy trial

Question	This study
Mouse or human?	Human: 18 autistic children aged 7 to 16, all with moderate to severe GI problems.
Correlation or cause?	It tested a treatment, but with no placebo group, so it can't separate the treatment's effect from expectations, attention, or time. Families and researchers knew everyone was treated, and the protocol bundled four parts (antibiotic, cleanse, acid reducer, donor microbes), so even if it helped, we can't tell which part did.
How many?	Very small: 18 treated children. Twenty non-autistic children were measured only for comparison of their microbes, not as a treatment control.
How long?	10 weeks of treatment plus 8 weeks of follow-up, with a later 2-year follow-up of the same children.
Who paid for it?	Mainly the Arizona Board of Regents, with extra funding from the Autism Research Institute and a Gordon and Betty Moore Foundation grant.
Is something being sold?	Not to the public, but several authors had pending or approved patents on using fecal transplants or probiotics for conditions including autism, and some received research funding from or consulted for a company working on fecal microbiota treatments (Crestovo), as the paper discloses.

The authors themselves called their study exploratory and said a double-blind, placebo-controlled trial was needed. What happened when one was done?

In 2024, Wan and colleagues reported a randomized, double-blind, placebo-controlled trial of oral fecal microbiota transplants in 103 autistic children in China (52 got the transplant, 51 got a placebo). Their main measure was a social-behavior rating scale. Both groups improved, and the difference between the transplant and placebo groups on that main measure was **not** statistically significant. The authors noted a substantial placebo effect.

(One secondary measure of social skills did favor the transplant group, but the authors described such secondary results as preliminary, and the trial was reported only as a short research letter.) An open-label study can't reveal a result like this: when everyone knows they're being treated, part of the improvement can come from expectations.

It's also worth asking what the goal of a treatment should be. Many autistic people and their allies question whether lowering scores on autism rating scales should be a treatment goal at all, since autism is a part of who someone is. Relieving constipation, belly pain, and diarrhea, on the other hand, is a goal everyone can agree on. That's why some newer trials measure gut symptoms as their main outcome (see the At the Bedside section).

Hype Meter: "Fecal transplants cure autism"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. The best-known study treated just 18 autistic children with GI problems in an open-label trial with no placebo group; GI symptoms improved, but the design can't show cause. A 2024 placebo-controlled trial of 103 autistic children found no significant difference from placebo on its main behavior measure. And autism is a lifelong neurodevelopmental difference, not a disease to cure. **What would change the grade:** Nothing would make "cure" the right word. For the separate question of whether microbiome treatments can ease *GI symptoms* in autistic people, large placebo-controlled trials with gut symptoms as the main outcome would give a real answer; right now that question is Preliminary.

This part takes practice



Open-label, placebo-controlled, sample size, bundled treatments: that's a lot of design vocabulary at once. If you remember just one question, make it this: "Compared with what?" An improvement only means something if a similar group that didn't get the treatment improved less.

13.8 When "Cure" Claims Cause Harm

Autism and ADHD attract a lot of products and programs that promise a cure. **Harmful cure claims** are promises that a product, diet, supplement, or procedure can cure or reverse autism or ADHD; they're unsupported by evidence and can cause harm through risky treatments, wasted money and time, missed care for real health problems, and the message that neurodivergent people need to be fixed.

Here's how harm can happen:

- **Physical risk.** Some "gut-healing" protocols involve antibiotics, bowel cleanses, or homemade fecal transplants. These are real medical interventions with real risks. The Kang trial was run under FDA oversight as an investigational treatment. Outside such oversight, things can go badly wrong: in 2019, the FDA reported that two adults with weakened immune systems developed serious infections from drug-resistant *E. coli* after receiving investigational fecal transplants from the same donor, and one of them died.

- **Restrictive diets.** Cutting out food groups can be especially risky for children who already eat a limited range of foods. Remember that autistic children on average already have lower calcium and protein intake.
- **Missed care.** Money and hope spent on an unproven "cure" can delay treatment for problems that do have good treatments, like constipation, sleep problems, or anxiety.
- **The message.** Constant talk of "curing" or "recovering from" autism tells autistic people that who they are is a disease. That message can hurt self-esteem and mental health.

Hype Meter: "Gut bacteria cause autism"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. One of the most carefully controlled human studies (247 children, 2021) found negligible direct links between autism and the microbiome once diet was considered, and a pooled analysis found autism-linked microbial patterns disappeared in sibling comparisons. The strongest causal evidence comes from mouse models, which can't capture what autism is. NIMH points to genes and early development, not gut bacteria. **What would change the grade:** Large studies that follow babies from birth, measure diet carefully, and show microbiome differences appearing *before* any signs of autism, replicated in several countries, would be needed to even reach Preliminary.

Watch for the slide from 'gut' to 'cure'



A common trick is to start with a true fact ("autistic kids have more constipation") and slide to a false one ("so fixing the gut fixes autism"). The first is a reason to treat constipation. It isn't a reason to believe the second.

13.9 ADHD and the Gut

Compared with autism, research on ADHD and the gut is younger and thinner.

A 2025 systematic review by Dias and colleagues found 14 studies on the gut microbiome in ADHD, with 1,319 participants, mostly children and teens aged 4 to 18, from Europe and East Asia. Some studies reported differences in particular bacteria (for example, less of a group called *Faecalibacterium*), but results on overall microbial diversity were inconclusive. As with autism, these are correlations, and diet, medications, sleep, and other factors could explain differences. Nobody has shown that gut bacteria cause ADHD.

What about sugar? The idea that sugar causes hyperactivity is one of the most widely believed food myths. In a 1995 meta-analysis in *JAMA*, Wolraich and colleagues pooled 23 studies in which children were given either sugar or an artificial sweetener, with neither the children, their parents, nor the researchers knowing which. They found that sugar did not affect children's behavior or thinking. The authors suggested that parents'

strong belief might come from expectation and from the settings where kids eat sugar (birthday parties are exciting with or without cake), while noting that a small effect, or effects in some individual children, could not be completely ruled out.

That's a good example of why blinding matters. If parents know their child just had sugar, their expectations can color what they see. Only a test where nobody knows who got sugar can separate expectation from a real effect.

So when Sam's older cousin posts that ADHD is "caused by sugar and a toxic gut," Sam can now answer: NIMH says genes play a large role in ADHD, blinded studies don't support the sugar idea, and gut microbiome studies in ADHD are small and inconsistent. Nico deserves good food, good sleep, and a comfortable gut like any kid. That's about health, not about "fixing" ADHD.

13.10 Care That Respects the Person

So what *does* the evidence support? It supports treating gut problems in autistic people and people with ADHD the same careful way we'd treat them in anyone, with extra attention to communication and sensory needs.

That might include:

- **Taking behavior changes seriously** as possible signs of pain, as the Buie recommendations suggest.
- **Using standard, proven approaches** for constipation, reflux, and belly pain, chosen by the care team.
- **Working with feeding specialists or dietitians** who respect sensory needs, rather than forcing foods.
- **Adjusting the doctor visit** with clear explanations, visual schedules, or extra time.
- **Watching mental health.** Anxiety and depression often co-occur with ADHD, according to NIMH, and NIMH is investing in research for autistic people with co-occurring mental health conditions. Chronic gut pain can add stress on top of that.

If you are struggling right now

If you are thinking about suicide or are in crisis, call or text **988** to reach the 988 Suicide & Crisis Lifeline (in the US), or go to the nearest emergency room. Outside the US, you can find a helpline at findahelpline.com. You can also talk to a parent, school counselor, or doctor.

For families

If your child is autistic or has ADHD and has gut symptoms, it's okay to push for those symptoms to be checked; they're a health issue, not "just part of autism." A sudden change in sleep, mood, or behavior can be a clue that something hurts, so it's worth writing down when changes happen and bringing notes to the doctor. Be cautious about programs that promise to "heal the gut" and "recover" your child, especially if they sell supplements, tests, or restrictive diets, and talk with your child's doctor before trying anything. Treating constipation or reflux can make your child more comfortable without changing who they are.

If you're going through this

If you're autistic or have ADHD and your stomach often hurts, you deserve care for that, just like anyone else. It's okay if it's hard to describe; you can point, type, rate pain with numbers or pictures, or bring notes to an appointment. You don't need to change who you are to feel better physically. If someone tells you a product will "fix" your autism or ADHD, you can say no and ask your care team what the evidence shows instead.

At the Bedside: When a Stomachache Looks Like Something Else

Meet the patient (fictional)

Leo is 12 and autistic. He loves maps and transit systems and uses speech for most things, though describing body sensations is hard for him. Over three months, his parents notice that he wakes up at night, melts down more often after school, eats even fewer foods than usual, and presses his belly against the table. His school reports he seems distracted and upset.

What the doctor checks: Leo's pediatrician asks about bowel habits, using a picture chart of stool types that Leo can point to, and asks his parents about diet, sleep, and when the changes started. She examines his belly gently, explaining each step first, and finds signs of a lot of stool in his colon. She looks for warning signs that would need more testing (such as blood in the stool, weight loss, or vomiting) and finds none.

Connecting the signals: The night waking, irritability, and belly pressing started around the same time as harder, less frequent stools. Leo's selective eating has narrowed further, which may mean less fiber and fluid. His interoceptive and communication differences make it harder for him to say "my stomach hurts," so the pain showed up as changes in sleep and behavior instead.

Diagnosis: Functional constipation (constipation without an underlying disease).

Why it happens: Constipation is common in autistic children, as the 2014 meta-analysis showed, and a narrow diet may contribute. When stool builds up, stretch signals from the colon travel to the brain and can cause

pain and discomfort. For Leo, those signals were real but hard to name.

The mind-body side: Leo's parents were worried his "behavior was getting worse." The care team helped them reframe it: Leo was communicating pain. The doctor tells the family clearly that treating constipation is about Leo's comfort and health, not about changing who he is. An occupational therapist suggests sensory-friendly ways to try new foods slowly, at Leo's pace. His parents work with him on a simple visual chart for rating stomach pain, so he has a tool to use next time.

Treatment today: The pediatrician recommends standard treatment for childhood constipation, which may include first clearing out the stool that has built up, then a daily medicine to keep stool soft, regular toilet routines, and gradual changes to fluids and fiber that work with Leo's food preferences. The family is told to follow the doctor's specific instructions rather than trying supplements or restrictive diets on their own. Within weeks, Leo is sleeping better and seems more like himself.

What's new in research: The Gut Bugs in Autism Trial in New Zealand, whose protocol was published in 2024 by Tweedie-Cullen and colleagues, plans to randomly assign 100 autistic teens and adults aged 16 to 45 with GI symptoms to receive either donor-microbe capsules or a placebo, with neither participants nor researchers knowing who gets which. Its main outcome is a GI symptom score at 6 weeks, a design focused on gut comfort and well-being. As of October 2026, its results had not been published, and the trial's University of Auckland study page still had no link to findings. **Evidence grade: Preliminary** for microbiome treatments as a way to ease GI symptoms in autistic people; this is an experimental approach, not standard care.

Your turn: reason through a variation

Nico, Sam's 10-year-old cousin with ADHD, starts complaining of stomachaches most mornings before school, but never on weekends. His older cousin says it's "leaky gut" and recommends a supplement. How would you reason about this?

Answer: The weekday-only pattern suggests something linked to school, such as worry, rushing breakfast, or skipping the bathroom in the morning. Stress can change gut sensations, as you learned in Chapter 7. ADHD often co-occurs with anxiety, so a doctor might ask about school stress as well as bowel habits. "Leaky gut" is not a diagnosis that explains this pattern, and a supplement isn't a substitute for a checkup. The right step is for Nico's parents to talk to his doctor, who can check for constipation or other causes and help with any school-related stress.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Autism is a disease that needs to be cured.
Reality: Autism is a lifelong neurodevelopmental difference. Autistic people may need support and may have health conditions worth treating, but autism itself is part of who they are, not an illness to remove.

Myth: Gut problems are just part of autism, so there's nothing to do about them.
Reality: GI symptoms are more common in autistic children, but they're separate health problems. Constipation, belly pain, and reflux can be treated with the same standard approaches used for other children.

Myth: The 2017 microbiota transfer study proved fecal transplants are a treatment for autism.
Reality: It was a small open-label study of 18 children with no placebo group. GI symptoms improved, but the design can't show cause, and a 2024 placebo-controlled trial of 103 children found no significant difference from placebo on its main behavior measure.

Myth: ADHD is caused by sugar or a bad diet.
Reality: NIMH says genes play a large role in ADHD. A 1995 meta-analysis of 23 blinded studies found that sugar did not affect children's behavior or thinking.

Myth: Different gut bacteria in autistic kids prove that bacteria cause autism.
Reality: A 2021 study of 247 children found that diet differences, linked to selective eating, explained most of the microbiome differences. Diet is a confounder.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "New research shows autism starts in the gut! Our probiotic blend helps kids recover. Thousands of happy parents!"

Grade: Hype. No human research shows that autism starts in the gut. One of the most carefully controlled studies (247 children) found that diet, not autism itself, explained most microbiome differences, and the strongest gut-behavior evidence comes from mouse models. "Recover" treats autism as a disease, and testimonials from parents are not controlled evidence, especially when a product is being sold. A careful version: "Autistic children have gut symptoms more often than other children, and those symptoms deserve standard medical care. There's no evidence that probiotics change autism."

2. Predict: A new study finds that autistic teens have lower microbial diversity than their non-autistic classmates. The researchers then compare autistic teens with their own non-autistic siblings who eat the same family meals. Predict what will happen to the difference, and explain why.

The difference will probably shrink or disappear. Siblings share family meals, home environment, and many other exposures, so comparing with siblings removes much of the confounding from diet and environment. That's what Morton and colleagues found in 2023: autism-linked microbial patterns showed up in age- and sex-matched comparisons but not in sibling-matched ones. If a difference remained even among siblings with similar diets, that would be more interesting.

3. Explain: Why might an autistic child with constipation show it through sleep problems or irritability instead of saying "my stomach hurts"?

Many autistic people have interoceptive differences, meaning they may notice or interpret internal signals like pain differently, and some find it hard to describe body sensations in words, especially in the moment. The pain signals from a stretched colon are still real, so discomfort may come out as night waking, irritability, or pressing on the belly. Expert recommendations note that GI problems in autistic children may show up as behavior changes, so caregivers should ask whether something hurts.

4. Apply: A parent group shares a study where 12 children took a supplement for 8 weeks, and parents reported that 9 of them "seemed calmer." Use the ideas of open-label trials, placebo control, and sample size to evaluate it.

It's very small (12 children), so the result could easily be chance. Parents knew their children were taking the supplement, so their ratings could be shaped by expectation, the same effect the sugar researchers suspected behind parents' beliefs about sugar. There's no placebo group, so we can't tell whether children would have "seemed calmer" anyway over 8 weeks. A better study would randomly assign many more children to the supplement or a look-alike placebo, with neither parents nor researchers knowing which.

5. Read the data. In a 2014 meta-analysis of 15 studies (McElhanon et al., *Pediatrics*), researchers compared GI symptoms in autistic children and comparison children. Here are the pooled odds ratios:

Symptom	Odds ratio
General GI symptoms	4.42
Constipation	3.86
Diarrhea	3.63
Abdominal pain	2.45

5. What does this data show, and what can't it show?

It shows that autistic children had higher odds of every GI symptom measured, from about 2.5 times for belly pain to about 4.4 times for general GI symptoms. It can't show why: the studies were observational, varied a lot in methods, and couldn't separate causes such as diet, sensory differences, medications, or how symptoms were reported. It also can't tell you about any individual child, since many autistic children have no GI problems. A useful follow-up would follow autistic and non-autistic children over time with the same symptom checklist and detailed diet records, to see whether diet explains part of the difference.

Exercises

Remember

1. What does "identity-first language" mean? Give one example.

Answer

Identity-first language puts the identity first, such as "autistic person" instead of "person with autism." Many autistic people prefer it because they see autism as a core part of who they are, though preferences vary, so it's best to use the words a specific person prefers.

1. According to the 2014 meta-analysis, roughly how much higher were the odds of general GI symptoms in autistic children than in comparison children?

Answer

About 4.4 times higher (odds ratio 4.42), based on 15 studies.

Understand

1. Explain what a confounding variable is, using diet and the microbiome in autism as your example.

Answer

A confounding variable is a third factor that affects both things being compared, creating a link that isn't direct. On average, autistic children eat a narrower range of foods (selective eating), and diet shapes gut bacteria. So autistic children have different microbiomes on average, even if autism itself doesn't directly affect the microbiome, as the 2021 Yap study suggested.

1. Explain why an open-label trial can't show that a treatment caused an improvement.

Answer

In an open-label trial, everyone knows who's being treated, and usually there's no placebo group for comparison. Improvements could come from expectations, extra attention, natural changes over time, or biased ratings by people who know about the treatment. Without a comparison group treated identically except for the real treatment, you can't separate those effects from the treatment's effect.

Apply

1. Use the Confounder Detective. Record the group difference with nothing accounted for, then with only Age, only Antibiotics, and only Diet variety accounted for. Which variable is the confounder, and how can you tell? Press New sample three times and describe how the leftover difference changes.
2. A news headline says: "Scientists find gut bacteria differences in kids with ADHD." Write three questions you would ask about the study before believing that bacteria cause ADHD, using ideas from this chapter.

Analyze

1. Compare the 2017 Kang open-label study (18 children) with the 2024 Wan placebo-controlled trial (103 children). For each, answer at least four of the six claim questions. Why might the open-label study have found improvements that the placebo-controlled trial didn't find relative to placebo?
2. The Hsiao 2013 mouse study and the Yap 2021 human study seem to point in different directions. Analyze what kind of question each can answer, and explain why a mouse result about "autism-like behaviors" can't settle whether gut bacteria cause autism in people.

Evaluate

1. A clinic advertises a "gut restoration program" that "helps children recover from autism," using antibiotics, a restrictive diet, and supplements. Evaluate this program using evidence from this chapter, considering safety, evidence quality, and the message it sends to autistic people.
2. Some researchers measure autism rating scales as the main outcome of microbiome treatment trials; others measure GI symptoms. Evaluate the two choices. Which outcome better fits a neurodiversity-affirming approach, and why?

Create

1. Design a study to test whether a microbiome treatment eases constipation in autistic teens. Describe your sample size, control group, blinding, main outcome, and how you would make participation comfortable for autistic participants (for example, communication and sensory needs).
2. Create a short, respectful guide (one page or a set of slides) for a pediatric clinic on "Recognizing gut pain in patients who communicate differently." Include at least three possible signs, two communication tools, and one sentence that explains why GI care is about comfort, not changing who someone is.

Key Takeaways

- Autism and ADHD are neurodevelopmental differences, not diseases to fix. NIMH points to genes and early development, not gut bacteria, as the main known influences. Identity-first language ("autistic person") is this book's default, but individual preferences come first.

- GI symptoms such as constipation, diarrhea, and belly pain are more common in autistic children (about 4.4 times the odds of general GI symptoms in a 2014 meta-analysis). They're real health problems that deserve standard, respectful care.
- Interoceptive and communication differences can make gut pain harder to recognize, so behavior changes may be a sign that something hurts. Selective eating is common and can narrow the diet.
- Diet is a confounder: a 2021 study of 247 children found negligible direct links between autism and the microbiome once diet was considered, and patterns found in another analysis disappeared in sibling comparisons.
- Mouse studies of maternal immune activation show that microbes can affect behavior-related traits in mice, but mouse "autism-like behaviors" are not autism.
- Open-label trials, small sample sizes, and bundled treatments can't prove cause. The 2017 microbiota transfer study (18 children, no placebo) is not proof of a treatment, and a 2024 placebo-controlled trial found no significant difference from placebo on its main measure.
- Claims that the gut causes or cures autism or ADHD, or that sugar causes ADHD, are Hype, and harmful cure claims can lead to risky treatments and hurtful messages.

You can separate a health problem from a headline!



You now know how to keep two questions apart: "Is this person's gut hurting?" and "Does the gut cause autism?" Next, in Chapter 14, we'll follow a different gut-brain mystery: the idea that Parkinson's disease might start in the gut for some people.

Help us get this chapter right

This chapter was written with care, but it was not written by autistic people or people with ADHD, and you are the experts on your own lives. If you're autistic or have ADHD (or both) and something here feels off, from a word choice to a missing perspective, please tell us through the Contact page. We'll read every message and list confirmed changes on the Accuracy page.

Quiz: Autism, ADHD, and the Gut

Test your understanding of Chapter 13. Choose the best answer, then click **Show Answer** to check.

Question 1

Which phrase is an example of identity-first language?

A. "A person with autism"

B. "A child who suffers from autism"

C. "An autistic person"

D. "A person who has recovered from autism"

Show Answer

The correct answer is **C**. Identity-first language puts the identity first, as in "autistic person," which many autistic people prefer because they see autism as part of who they are. Option A is person-first language, which some people prefer, so the best rule is to use the words a specific person chooses. Options B and D frame autism as a disease, which this chapter avoids.

Concept Tested: Identity-First Language **Bloom's Level:** Remember

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Question 2

In the 2014 meta-analysis of 15 studies, how did the odds of general GI symptoms in autistic children compare with comparison children?

A. About 4.4 times higher

B. About the same

C. About half as high

D. About 40 times higher

Show Answer

The correct answer is **A**. The pooled odds ratio for general GI symptoms was 4.42. That is a large, consistent association, but the study could not show why the symptoms were more common. Option D exaggerates the result roughly tenfold, the kind of error that spreads in headlines.

Concept Tested: GI Symptoms in Autism **Bloom's Level:** Remember

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Question 3

What is an open-label trial?

A. A study in which neither participants nor researchers know who gets the real treatment

B. A study that tests a treatment only in mice

C. A study that compares a treatment with a look-alike placebo

D. A study in which participants and researchers know who is getting the treatment, usually with no placebo group

Show Answer

The correct answer is **D**. In an open-label trial, everyone knows who is treated, so improvements could come from expectations, attention, or time passing. Option A describes a double-blind design, which is the opposite, and option C describes a placebo-controlled trial.

Concept Tested: Open-Label Trial **Bloom's Level:** Remember

Question 4

Which statement best describes the idea of neurodiversity?

A. Autism and ADHD are diseases that should be cured as early as possible.

B. Natural variation in how brains develop and work, including autism and ADHD, is part of human diversity, so the goal is understanding and support.

C. Neurodivergent people never need any help or health care.

D. Only people with ADHD are neurodivergent.

Show Answer

The correct answer is **B**. Neurodiversity treats differences like autism and ADHD as part of normal human variation, calling for support and accommodation rather than cure. Option C is a common misunderstanding: the neurodiversity view still recognizes real challenges and co-occurring health problems, such as gut pain, that deserve care.

Concept Tested: Neurodiversity **Bloom's Level:** Understand

Question 5

Why might gut pain in some autistic children go unnoticed for a long time?

A. Interoceptive and communication differences can make internal pain harder to notice or describe, so it may show up as changes in sleep or behavior.

B. Autistic children cannot feel pain.

C. GI problems never happen in autistic children.

D. Doctors are not allowed to examine autistic children.

Show Answer

The correct answer is **A**. Many autistic people notice or interpret internal signals differently, and describing body sensations can be hard, so discomfort may appear as night waking, irritability, or pressing on the belly. Option B is false and harmful: the pain signals are real; the difference is in how they're noticed or expressed.

Concept Tested: Interoceptive Differences **Bloom's Level:** Understand

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Question 6

How can selective eating help explain why autistic children's gut microbiomes differ on average from other children's?

A. Selective eating directly changes a person's genes.

B. Selective eating is caused by gut bacteria.

C. A narrower diet feeds a narrower range of gut bacteria, so diet differences can create microbiome differences.

D. Selective eating has no effect on the gut.

Show Answer

The correct answer is **C**. Autistic children on average have higher odds of feeding problems, and diet shapes the microbiome, so a less varied diet can mean less diverse gut bacteria. Option B reverses the arrow; the 2021 Yap study supported the chain from autism-related preferences to diet to microbiome, not microbes causing eating patterns.

Concept Tested: Selective Eating **Bloom's Level:** Understand

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Question 7

A company says 10 children took its gut supplement for 6 weeks and their parents rated them as "much calmer." There was no comparison group. What is the biggest problem with this evidence?

A. Six weeks is too long for any study.

B. With only 10 children and no placebo group, the change could be due to chance or parents' expectations rather than the supplement.

C. Parents are never allowed to rate their children.

D. The supplement must have worked because most children improved.

Show Answer

The correct answer is **B**. A tiny sample swings easily by chance, and parents who know their child is taking a supplement may see what they expect. A placebo-controlled trial with many more children, where neither parents nor researchers know who got what, would be needed. Option D is the trap the company wants you to fall into.

Concept Tested: Sample Size **Bloom's Level:** Apply

Question 8

A website promises that its "gut detox program," with antibiotics, a restrictive diet, and homemade fecal transplants, will help children "recover from autism." Which concern from this chapter is MOST important?

A. The program is probably too expensive, but otherwise fine.

B. It should be tried first, since there's nothing to lose.

C. The program is fine if it has many positive reviews.

D. It's a harmful cure claim: it treats autism as a disease, lacks evidence, and uses risky interventions such as unsupervised fecal transplants and restrictive diets.

Show Answer

The correct answer is **D**. There's no evidence that any program cures autism, and the components carry real risks; the FDA reported in 2019 that a person died after a drug-resistant infection was passed on through an investigational fecal transplant. Restrictive diets can add to nutrient gaps in children who already eat a narrow range of foods. Option B is wrong because there is a lot to lose: safety, money, time, and a child's sense of being accepted.

Concept Tested: Harmful Cure Claims **Bloom's Level:** Apply

Question 9

In a study, autistic children have lower microbiome diversity than comparison children. After researchers account for diet variety, the difference nearly disappears; accounting for age changes almost nothing. What is the best interpretation?

A. Diet variety is a confounder that explains most of the difference, while age is balanced between groups and isn't.

B. Autism directly lowers microbiome diversity.

C. Age is the main cause of the difference.

D. Low microbiome diversity causes autism.

Show Answer

The correct answer is **A**. A confounder differs between groups and affects the outcome; when it's accounted for, the apparent group difference shrinks. Age affects diversity but is spread evenly across groups, so it can't explain the gap. This mirrors the 2021 Yap study. Option D reverses the direction and ignores the confounder.

Concept Tested: Diet as Confounder **Bloom's Level:** Analyze

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Question 10

In the maternal immune activation (MIA) mouse study, a gut bacterium improved some "autism-like behaviors" in the offspring. Why doesn't this show that probiotics would help autistic people?

A. Because the mice were too young

B. Because the bacterium used was not a real bacterium

C. Because no studies have ever been done in mice

D. Because a lab-triggered mouse model with "autism-like behaviors" is not human autism, and mouse results often don't carry over to people

Show Answer

The correct answer is **D**. The MIA model triggers an immune response on purpose in pregnant mice, and the behaviors measured are only loose stand-ins for parts of human experience. Results in mice are reasons to ask questions, not evidence for treating people. Option C is simply false; this was itself a mouse study.

Concept Tested: Maternal Immune Activation **Bloom's Level:** Analyze

Chapter 14: Parkinson's, Alzheimer's, and the Gut

Summary

Parkinson's disease is best known for tremor and slow movement, but many people have gut problems, especially constipation, years before any movement symptoms appear. This chapter explains how Parkinson's damages dopamine neurons, how a misfolded protein called alpha-synuclein may spread from cell to cell, and why some scientists think the disease can sometimes begin in the gut and travel up the vagus nerve. You will weigh the evidence from autopsy studies, mouse experiments, and large health-record studies of people who had their vagus nerve cut or their appendix removed, and you will compare the "gut-first" and "brain-first" ideas side by side. The chapter ends with Alzheimer's disease, where gut microbe research is much younger, and with practical points about how the gut affects Parkinson's medicine.

Concepts Covered

1. Neurodegeneration
2. Parkinson's Disease
3. Dopamine Neuron Loss
4. Alpha-Synuclein
5. Lewy Body
6. Prodromal Symptoms
7. Constipation
8. Braak Hypothesis
9. Prion-Like Spread
10. Gut-First Subtype
11. Brain-First Subtype
12. Truncal Vagotomy Studies
13. Appendix and Parkinson's
14. Levodopa Absorption
15. Alzheimer's Disease
16. Amyloid Beta

Prerequisites

- Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading) for the enteric nervous system
- Chapter 2: The Vagus Highway for the vagus nerve and the brainstem
- Chapter 3: Meet the Microbiome for gut microbes and correlation versus cause
- Chapter 13: Autism, ADHD, and the Gut for confounding and small studies

A mystery that starts far from the brain



Parkinson's and Alzheimer's are brain diseases, so why would a gut book spend a whole chapter on them? Because one of the biggest open questions in neurology right now is whether Parkinson's sometimes starts in the gut and climbs up the vagus nerve. (That's me!) Many families, maybe yours, are touched by these diseases, and the online claims about them run far ahead of the evidence. Let's check the evidence together.

14.1 Riya's Grandfather and a Clue From Years Ago

Riya's grandfather, whom she calls Nanaji, is 72. Two years ago his right hand started shaking when it rested in his lap, and his walk turned into small, shuffling steps. His neurologist diagnosed Parkinson's disease. At a family dinner, Riya's grandmother mentioned something odd: "His stomach trouble started long before the shaking. He was constipated for years, and he stopped being able to smell my cooking." Riya, who had just learned in biology club that the gut has its own nervous system, sat up. Could a brain disease have started in the gut? (Riya and her family are fictional and appear throughout this book.)

Riya's question is a real one that scientists are arguing about right now. Her grandmother's observation matches a pattern doctors have noticed in many people with Parkinson's: gut problems, smell loss, and certain sleep problems often show up years before any shaking. This chapter follows that clue. We'll see where the evidence is strong, where it is mixed, and where it turns into hype.

Here's the plan. First, what goes wrong in the brain in Parkinson's. Then the early clues, the idea that the disease can travel from gut to brain, and the experiments that test it in mice and people. Finally, Alzheimer's disease, where the gut story is younger and less certain.

14.2 When Brain Cells Wear Out: Neurodegeneration

Picture a row of old houses on a street. Most stay standing for a century. But in one neighborhood, the houses start to fall apart one after another, and the damage seems to move from one house to its neighbors. That's a rough picture of what happens in some brain diseases.

Neurodegeneration is the slow, progressive loss of the structure and function of neurons, ending in their death, in particular parts of the nervous system. "Progressive" means it gets worse over time. Neurons in the

adult brain are mostly not replaced when they die, so the loss adds up. Parkinson's disease and Alzheimer's disease are the two most common neurodegenerative diseases, and both mostly affect older adults.

You already know the basics of neurons and how they signal to each other. If you'd like a deeper review of how the aging brain changes and how these diseases affect it, see From Neuron to Bedside, Chapter 13. For how the brain controls movement, see From Neuron to Bedside, Chapter 7.

14.3 Parkinson's Disease: Losing the Dopamine Neurons

Parkinson's disease (PD) is a progressive disorder of the nervous system that mainly affects movement, caused by the gradual damage and death of nerve cells in certain parts of the brain. The National Institute of Neurological Disorders and Stroke (NINDS) lists four common movement symptoms:

- **Tremor:** rhythmic shaking, often starting in one hand and most obvious when the hand is at rest. Some people with PD never develop a tremor.
- **Rigidity:** muscles that stay tight and stiff.
- **Bradykinesia:** slowness of movement, so everyday tasks like dressing take longer, and the face may show less expression.
- **Postural instability:** balance problems that raise the risk of falls.

Why these symptoms? Deep in the brain is a small region called the substantia nigra ("black substance," because its cells look dark). Its neurons make dopamine, a chemical messenger that helps the brain produce smooth, purposeful movements. **Dopamine neuron loss** is the death of these dopamine-making neurons in the substantia nigra, the main cause of the movement symptoms of Parkinson's. According to NINDS, by the time movement symptoms appear, most people have already lost 60 to 80% or more of these cells.

Read that number again. The brain has a lot of backup capacity, so it can lose most of these neurons before anything looks wrong from the outside. That means the disease process has been running quietly for a long time before diagnosis. This is the window where the gut clues live.

Parkinson's is not only about dopamine. NINDS notes that people with PD also lose cells that make norepinephrine, a messenger the body uses for automatic jobs like keeping blood pressure steady. That may explain some symptoms that aren't about movement, such as tiredness and blood pressure changes. NINDS also lists other symptoms: depression or anxiety (sometimes even before movement problems), sleep problems, speech changes, bladder problems, and digestive problems like nausea and constipation.

Who gets Parkinson's? NINDS says the average age when symptoms start is the early to mid-60s, and the chance rises with age. A small percentage of people get "early-onset" PD at younger ages. In most people the cause is unknown; researchers think both genes and environmental exposures play a part.

14.4 A Protein That Folds Wrong: Alpha-Synuclein and Lewy Bodies

Proteins are like long strings that must fold into exact shapes to work, the way a paper airplane only flies if it's folded correctly. Crumple it the wrong way, and it's useless. Worse, some wrongly folded proteins stick together into clumps.

Alpha-synuclein is a protein found in neurons, especially at their tips where they send signals, that can misfold and clump together; these clumps are a hallmark of Parkinson's disease. In healthy neurons it is thought to help with releasing chemical messengers, though its normal job is still being studied.

When alpha-synuclein misfolds, it forms clumps inside neurons. A **Lewy body** is an abnormal round clump, made mostly of misfolded alpha-synuclein, found inside nerve cells in Parkinson's disease and some related conditions. NINDS says damaged brain cells in most people with PD have Lewy bodies, though researchers don't yet know exactly why they form or how much harm they do themselves. Pathologists also see thinner threads of the same protein in nerve fibers, called Lewy neurites. Together, these are what scientists mean by "Lewy pathology."

Here's the part that made scientists think about the gut. In some diseases, a misfolded protein can act like a bad template. When it touches a normal copy of the same protein, it can push that copy to misfold too, and the misfolding spreads.

Prion-like spread is the idea that a misfolded protein, such as alpha-synuclein, can pass from one neuron to a connected neuron and make normal copies of the protein misfold, so the damage moves along nerve pathways over time. The name comes from prions, the misfolded proteins behind mad cow disease. "Prion-like" does **not** mean Parkinson's is contagious between people. It describes how the protein may spread from cell to cell inside one person's nervous system.

Think of falling dominoes. The first domino tips the next, which tips the next, and the wave follows the line of dominoes wherever it goes. In 2003, the German neuroanatomist Heiko Braak and his colleagues used that very image, a falling row of dominoes, to describe how Lewy pathology seems to march through connected brain regions in a set order. If the dominoes follow nerve connections, then where is the first domino? That question leads straight to the gut.

Lots of new protein words



Alpha-synuclein, Lewy bodies, prion-like spread: that's a lot at once. Here's my shortcut: alpha-synuclein is the protein, a Lewy body is the clump it forms, and prion-like spread is the idea that the clumping moves from neuron to neuron like dominoes.

14.5 Clues Before the Tremor: Prodromal Symptoms

Doctors use the word "prodrome" for early warning signs that come before the main symptoms of a disease. **Prodromal symptoms** are early signs that can appear years before the main symptoms of a disease and

before it can be diagnosed; in Parkinson's they include constipation, loss of smell, acting out dreams during sleep, and mood changes.

The National Institute on Aging (NIA) says many people with Parkinson's notice that before their stiffness and tremor began, they had sleep problems, constipation, loss of smell, and restless legs. NINDS adds that depression or anxiety may appear early, even before movement problems. One sleep problem gets special attention: REM sleep behavior disorder (RBD), in which a person physically acts out vivid dreams, kicking, punching, or shouting, because the normal "freeze" of the muscles during dreaming sleep doesn't work.

The table below collects the main prodromal signs you just read about. Notice that none of them is about movement.

Early sign	What the person notices	Part of the nervous system that may be involved
Constipation	Fewer, harder bowel movements	Gut nerves (enteric nervous system) and the vagus nerve
Loss of smell	Food tastes flat; can't smell smoke or flowers	Smell centers in the brain
REM sleep behavior disorder	Acting out dreams, sometimes injuring a bed partner	Brainstem circuits that control sleep
Depression or anxiety	Low mood, worry	Several brain systems, including ones that make serotonin and norepinephrine

Constipation: the most famous gut clue

Constipation means having fewer bowel movements than usual (often fewer than three a week), or stools that are hard, dry, or difficult to pass. It's very common. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) says about 16 out of 100 adults have constipation symptoms, rising to about 33 out of 100 adults aged 60 and older. It usually has ordinary causes, like low fiber, not enough fluid, travel, stress, or certain medicines.

So how strong is the link to Parkinson's? In 2016, Adams-Carr and colleagues combined 9 observational studies including 741,593 people. People with constipation had about twice the odds of being diagnosed with Parkinson's later (an odds ratio of 2.27). Even when they looked only at constipation that started **more than 10 years** before diagnosis, the link held (an odds ratio of 2.13). Doctors had already recognized constipation as a non-motor feature of Parkinson's; this study showed it can come more than a decade before diagnosis.

Now the most important part, especially if you or someone you love is constipated. An odds ratio of about 2 is a **relative** number. It compares two groups. It does not tell you that constipation is likely to lead to Parkinson's.

Parkinson's is uncommon, so doubling a small chance still gives a small chance. The great majority of constipated people never develop Parkinson's. Constipation is a clue that researchers can study across huge groups of people, not a warning sign for any one person.

Twice as likely, but of what?



Whenever you hear "twice as likely," ask "twice as likely as what?" Doubling a small chance still leaves a small chance, and that's exactly why constipation tells researchers a lot about Parkinson's while telling a single constipated teen almost nothing.

Notice what kind of evidence this is: observational studies of people, showing a correlation over time. Constipation coming first fits the idea that the gut is involved early. But it could also mean that the disease affects many parts of the nervous system at once, and gut nerves simply show it first. Timing alone can't prove where the disease began.

14.6 The Braak Hypothesis: Does the First Domino Fall in the Gut?

In 2003, Braak's team published two influential papers. In the first, they examined the brains of many people who had died with Parkinson's, and of some people who had Lewy pathology but had never shown symptoms. They proposed a staging system. Lewy pathology, they reported, first shows up in two places: a cluster of neurons low in the brainstem that sends fibers down the vagus nerve (the dorsal motor nucleus of the vagus), and a smell-processing area at the front of the brain. From the brainstem, the pathology seems to climb upward through connected regions, reaching the substantia nigra in the middle stages and the outer brain (the cortex) last.

The second paper made a bolder suggestion. Some people who had no symptoms already had Lewy pathology in both the gut's nervous system and the brainstem vagus nucleus. Braak's team asked whether an unknown trigger, perhaps something swallowed, might cross the gut lining, get into enteric neurons, and travel up the vagus nerve into the brain, tipping dominoes all the way.

The **Braak hypothesis** is the proposal, published by Heiko Braak and colleagues in 2003, that Parkinson's pathology spreads through the nervous system in a predictable order, beginning low in the brainstem and in the smell system, and that in some cases it may start in the gut and travel up the vagus nerve to the brain. Notice the two parts: a **staging pattern** in the brain (based on what they saw at autopsy) and a **gut origin idea** (a hypothesis about where it starts).

Why was this exciting? It tied together several puzzles. It explained why constipation and smell loss can come years before movement symptoms, and why the vagus nucleus is hit so early. It also suggested new ways to detect Parkinson's early, perhaps by sampling gut tissue, long before the dopamine neurons are mostly gone.

Why is it still a hypothesis? Autopsy studies show where pathology is at the moment of death, not where it started. It's like finding fallen dominoes after the fact: you can guess where the first one fell, but you didn't see

it fall. And not every brain fits the pattern. In 2019, Borghammer and Van Den Berge pointed out that a small fraction of people with Parkinson's don't have pathology in the vagus nucleus at all, which is hard to explain if every case climbs up from the gut.

Here's how this book grades the popular version of the idea.

Hype Meter: "Parkinson's can start in the gut"

Strong	**Moderate**	Preliminary	Hype

Verdict: Moderate (as a hypothesis for some patients). Human autopsy studies show Lewy pathology early in the vagus nucleus and sometimes in gut nerves, large observational studies show constipation can come more than 10 years before diagnosis, and mouse experiments show misfolded alpha-synuclein can travel from gut to brain along the vagus nerve. But human evidence is mostly correlation, studies of vagus surgery and appendix removal in people disagree, and some patients don't fit the pattern at all. Saying "Parkinson's starts in the gut" for everyone is too strong; "Parkinson's may start in the gut in some people" is a fair summary, and that narrower claim is what this grade covers. **What would change the grade:** Long-term human studies that track alpha-synuclein in the gut and brain of the same people over many years, and show the gut changes come first and predict who develops the disease, could move it up. Large studies showing no gut-first group would move it down.

You can find how each grade is defined on the Hype Meter page.

14.7 Testing the Idea in Mice

If the dominoes really can fall from the gut to the brain, you should be able to start them in the gut on purpose and watch. You can't do that in people, but you can in mice.

In 2019, a team at Johns Hopkins led by Sangjune Kim, Ted Dawson, and Han Seok Ko did exactly that. They made small, pre-formed fibers of misfolded mouse alpha-synuclein (called "seeds") and injected them into the muscle wall of the upper gut of mice. Then they looked at the brains at 1, 3, 7, and 10 months.

The misfolded protein showed up first in the vagus nucleus of the brainstem, then in other parts of the lower brainstem, and much later in regions including the amygdala and the substantia nigra. The mice gradually lost dopamine neurons and developed movement problems as well as non-movement problems, such as poorer scores on memory and smell tests. Then came the key test. In mice whose vagus nerve was cut (a truncal vagotomy), and in mice bred without the alpha-synuclein protein, the spread to the brain didn't happen, and neither did the neuron loss.

How to read a gut-brain claim: the 2019 gut-to-brain mouse study

Question	This study
Mouse or human?	Mouse only. No people were studied.
Correlation or cause?	Cause, within the mouse model. Researchers injected seeds on purpose and showed that cutting the vagus nerve, or removing alpha-synuclein, blocked the spread. But the seeds were injected by a needle, which is not how Parkinson's begins in people.
How many?	Small groups: about 7 to 12 mice per group in the behavior tests.
How long?	Up to 10 months after injection, which is a large part of a mouse's life.
Who paid for it?	The JPB Foundation and the US National Institutes of Health (National Institute of Neurological Disorders and Stroke), with support from the Adrienne Helis Malvin Medical Research Foundation. The authors declared no competing interests.
Is something being sold?	No. This was basic research with no product.

The conclusion: this careful experiment shows that the gut-to-brain route is **possible** in mice, and that the vagus nerve can carry misfolded alpha-synuclein. It does not show that this is how Parkinson's starts in people, or how often. The first domino in a human, if it is in the gut, would not be a needle full of lab-made protein.

A second famous mouse study came from Caltech in 2016. Sampson and colleagues used mice engineered to make too much alpha-synuclein. Mice raised germ-free (with no microbes) or treated with antibiotics had fewer movement problems, while adding gut microbes back made the problems worse. Mice that received gut microbes from people with Parkinson's developed worse movement problems than mice that received microbes from healthy donors. This suggests gut microbes can **influence** how a Parkinson's-like disease plays out in this mouse model. It does not show that microbes cause Parkinson's in people.

A mouse is not a mini-person



When a headline says "Scientists prove Parkinson's starts in the gut," check whether the study used mice. These two studies are strong experiments, but they show what can happen in a mouse model, not what does happen in people.

14.8 Testing the Idea in People: Vagus Surgery and the Appendix

Scientists can't cut people's vagus nerves to test a hypothesis. But for decades, surgeons cut the vagus nerve for another reason: to reduce stomach acid in people with severe ulcers, before modern ulcer medicines made the operation rare. (Chapter 2 tells that story.) That history created a natural experiment.

Truncal vagotomy studies are large health-record studies that compare people who had their main vagus nerve trunks surgically cut (a truncal vagotomy, usually for ulcers) with people who did not, to test whether cutting the gut-to-brain vagus route lowers the later risk of Parkinson's disease. A "selective" or "superselective" vagotomy cuts only some branches, so it acts as a useful comparison: if the vagus route matters, a full cut should protect more than a partial one.

Here's what two big studies found.

- **Denmark, 2015 (Svensson and colleagues).** The team used national registries of people who had a vagotomy between 1977 and 1995. Overall, truncal vagotomy was not clearly linked to Parkinson's risk (a hazard ratio of 0.85, a result that could easily be chance). But among people followed for more than 20 years, those with a truncal vagotomy had about half the risk of the general population (a hazard ratio of 0.53). The researchers noted that the estimates weren't very precise, and the confidence interval for that result came very close to "no difference." Superselective vagotomy showed no change.
- **Sweden, 2017 (Liu and colleagues).** This larger study compared 9,430 people who had a vagotomy (3,445 truncal) with 377,200 matched people. Overall, vagotomy was **not** linked to Parkinson's risk (a hazard ratio of 0.96). There was only a suggestion of lower risk after truncal vagotomy (0.78, which could be chance), and a lower risk when the truncal vagotomy happened at least 5 years before diagnosis (0.59).

So: some, but not all, results point the way the gut-first idea predicts, and the clearest signals come from small subgroups. These are also observational studies. People who needed vagus surgery may differ from other people in smoking, diet, other illnesses, or medicines, and those differences could affect Parkinson's risk too. The Danish team did adjust for several of these, but no adjustment is perfect.

Vagus surgery is also not a way to prevent Parkinson's. The operation has real side effects (Chapter 2's bedside case describes some), and the evidence doesn't come close to supporting it as prevention.

The appendix puzzle

The appendix is a small, finger-shaped pouch attached to the large intestine, packed with immune tissue and nerves. **Appendix and Parkinson's** refers to the research question of whether removing the appendix (an appendectomy) changes a person's later risk of Parkinson's disease, based on the idea that the appendix might store misfolded alpha-synuclein that could seed the disease.

The results are a good lesson in why one study is never the final word.

Study	What it found
Killinger et al. 2018 (two data sets, more than 1.6 million people)	Appendix removal decades before diagnosis was linked to **lower** Parkinson's risk. Healthy human appendixes also contained clumped alpha-synuclein.
Svensson et al. 2016 (Denmark, 265,758 people with appendectomy)	Appendix removal was linked to a **slightly higher** risk (hazard ratio 1.14).
Lu et al. 2020 meta-analysis (6 studies, about 3.55 million people)	**No** overall link (relative risk 1.02).
Chin et al. 2025 meta-analysis (9 studies)	**No** overall link (relative risk 1.01).

The 2018 study made headlines around the world. But when researchers pooled all the available studies, the effect disappeared. The finding that healthy appendixes contain clumped alpha-synuclein is still interesting, because it shows the gut can hold the protein in its problem form. But it doesn't mean the appendix starts the disease, and removing it doesn't seem to change risk overall.

Hype Meter: "Removing your appendix prevents Parkinson's"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. One large 2018 study linked appendix removal to lower Parkinson's risk, but a Danish study of 265,758 people found a slightly higher risk, and two meta-analyses (6 studies with about 3.55 million people, and 9 studies in 2025) found no overall link. No study tested appendix removal as prevention, and surgery has its own risks. **What would change the grade:** New, large studies that consistently find lower risk after appendix removal, with a clear biological explanation, could move the association to Preliminary. Even then, it would not make surgery a prevention strategy.

If you're going through this

If you have a gut condition like IBS, Crohn's, or ulcerative colitis, reading about constipation and Parkinson's might make you worry. Please hold onto the numbers: Parkinson's mostly begins in older adults, the constipation link comes from comparing huge groups, and most people with gut symptoms never develop it. Your gut condition is its own diagnosis with its own care plan. If you're worried, write the question down and ask your care team; they can explain what your symptoms do and don't mean.

14.9 Two Routes? Gut-First and Brain-First Parkinson's

If some patients fit Braak's climb from the brainstem and others don't, maybe there's more than one kind of Parkinson's. In 2019, the Danish researcher Per Borghammer and his colleague Nathalie Van Den Berge proposed exactly that.

The **gut-first subtype** (also called "body-first") is a proposed form of Parkinson's disease in which alpha-synuclein pathology starts in the gut or other body nerves, reaches the brainstem through the vagus nerve, and climbs up to the dopamine neurons later. Because the body's automatic nerves and the brainstem sleep circuits are damaged early, this subtype is predicted to have constipation, other automatic-nerve problems, and REM sleep behavior disorder years **before** movement symptoms.

The **brain-first subtype** is a proposed form of Parkinson's disease in which alpha-synuclein pathology starts inside the brain, reaches the dopamine system early, and spreads down to the brainstem and the body's nerves later. This subtype is predicted to show movement symptoms earlier, with REM sleep behavior disorder and gut problems usually absent before diagnosis and appearing later, if at all.

Before we compare them, notice that both subtypes share the same machinery from Section 14.4: misfolded alpha-synuclein and prion-like spread along nerve connections. What differs is where the first domino falls. The table below lays out the predictions.

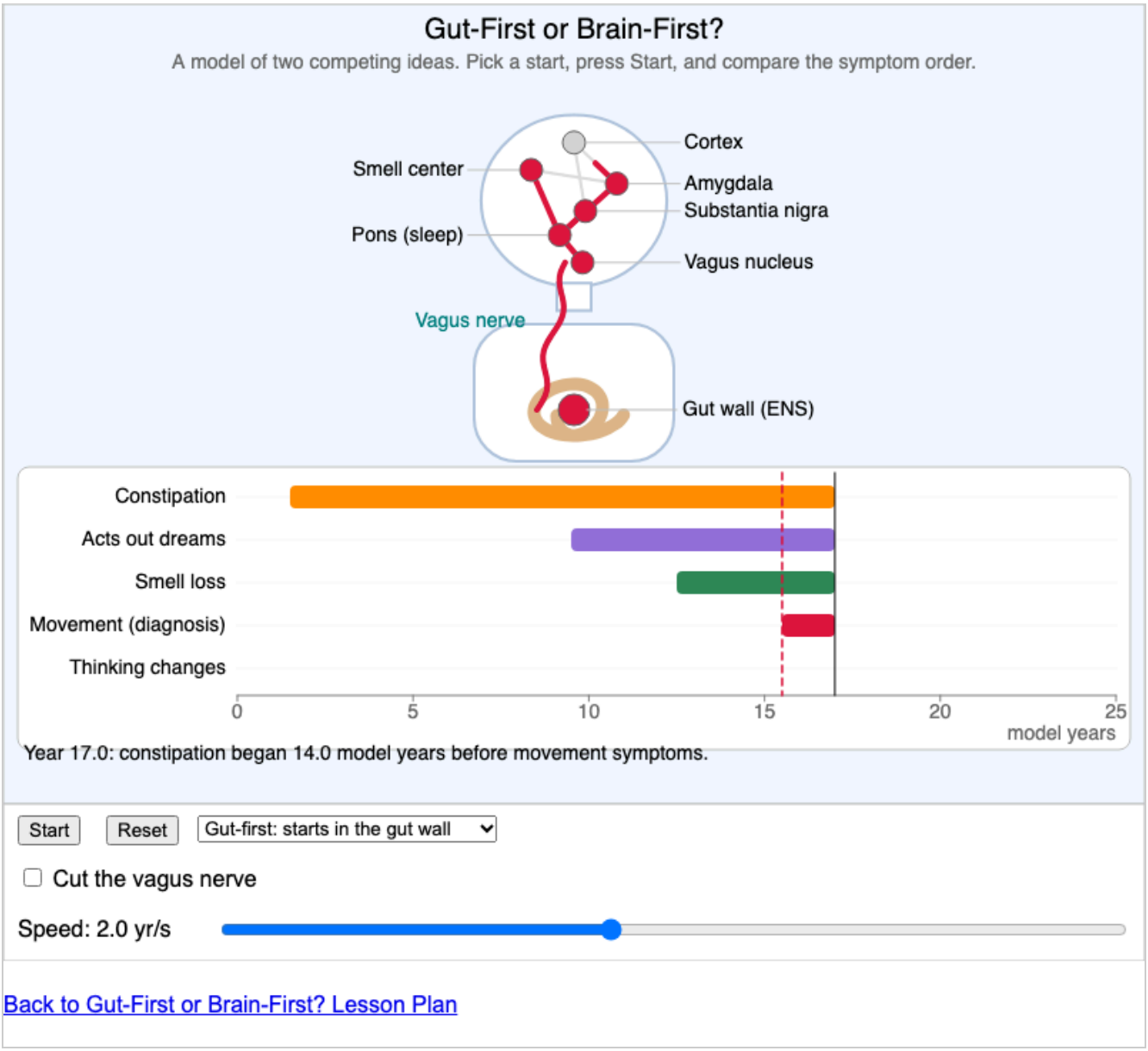
Feature	Gut-first subtype	Brain-first subtype
Proposed starting place	Gut or other body nerves	Inside the brain (the exact site is debated)
Route to the dopamine neurons	Up the vagus nerve, through the brainstem	Directly within the brain
Constipation and other automatic-nerve problems	Early, often years before diagnosis	Later

Feature	Gut-first subtype	Brain-first subtype
REM sleep behavior disorder before diagnosis	Common	Usually absent
Movement symptoms	Come later in the sequence	Come earlier in the sequence

Borghammer and Van Den Berge supported their proposal with brain imaging studies comparing people with and without REM sleep behavior disorder, plus autopsy findings, and noted that it could explain several puzzles in the earlier research. But they called it a hypothesis themselves, a framework for designing new studies. It is one of the most active debates in Parkinson's research.

The MicroSim below lets you compare the two routes. In it, "pathology" means misfolded alpha-synuclein building up in a region, and a symptom appears on the timeline once a region is damaged enough. The years are made-up teaching numbers, chosen only to show the order of events each idea predicts.

Diagram: Gut-First or Brain-First?



[Back to Gut-First or Brain-First? Lesson Plan]

Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch14-two-routes/main.html

Open the Gut-First or Brain-First? MicroSim fullscreen

MicroSim specification: Gut-First or Brain-First?

Type: microsim **sim-id:** ch14-two-routes
Library: p5.js
Status: Implemented
Bloom Level: Analyze, Evaluate
Bloom Verb: compare
Learning Objective: The learner will compare the gut-first and brain-first hypotheses of Parkinson's disease by the order of early symptoms each predicts, and explain why cutting the vagus nerve matters only in the gut-first route.

Canvas: 560 px drawing area plus 110 px controls (iframe 672 px); responsive to about 380 px wide.

Controls: Start/Pause, Reset; Starting point select (Gut-first: starts in the gut wall; Brain-first: starts inside the brain); "Cut the vagus nerve" checkbox; Speed slider (0.5 to 4 model years per second).

Rules: Seven regions (gut wall, vagus nucleus, pons sleep circuits, smell center, amygdala, substantia nigra, cortex) connected by edges with illustrative travel delays. Pathology arrives at each region along the shortest path from the starting point; a symptom bar starts 1.5 model years after arrival (gut wall: constipation; pons: acting out dreams; smell center: smell loss; substantia nigra: movement symptoms, marked as diagnosis; cortex: thinking changes). Cutting the vagus nerve removes the gut to vagus nucleus edge.

Feedback: A body diagram colors regions by pathology level and draws spread along connections; a symptom timeline (0 to 25 model years) shows bars and a dashed diagnosis line; a status line reports how many years before diagnosis constipation appeared.

Provenance: Braak et al. 2003; Borghammer and Van Den Berge 2019; Kim et al. 2019 (vagotomy blocked spread in mice). All timings are illustrative. Labeled on screen as a model of competing ideas.

Start with **Gut-first** and press Start. Watch the red pathology climb from the gut wall up the vagus nerve to the brainstem, then to the sleep circuits and smell center, and only much later to the substantia nigra. On the timeline, constipation and dream-acting appear long before the dashed "diagnosis" line. Then switch to **Brain-first** and run it again. Movement symptoms come early, and constipation shows up last, after the disease has worked its way down to the body.

Now test a prediction. Check **Cut the vagus nerve** and run each route. In the gut-first route, the spread stays in the gut, which mirrors what happened in the 2019 mouse study. In the brain-first route, cutting the vagus changes nothing in the brain, because the disease never needed that road. Ask yourself: if the human vagotomy studies had found a big, clear protective effect, which hypothesis would that support? What does the mixed result you read in Section 14.8 suggest?

What this model leaves out

- It is a model of two competing hypotheses, not a proven map. Many scientists think real Parkinson's is messier, and some think neither route explains every case.
- The years, the regions chosen, and the order of connections are simplified teaching values; real timelines vary widely from person to person, and nobody can watch the spread happen in a living human.
- Real spread involves both sides of the brain, many more regions, and probably genes, aging, inflammation, and the environment, which the model ignores.
- In the model, cutting the vagus fully blocks gut-first spread, as it did in mice; human vagotomy studies give mixed results, and other nerve routes may exist.
- Symptoms appear at a single fixed threshold here. In real life, symptoms like constipation and low mood have many other causes, and many people with them never develop Parkinson's.

14.10 The Gut Matters for Treatment Too: Levodopa Absorption

Even if Parkinson's turns out to start in the brain for most people, the gut still matters every day for people living with it, because of how the main medicine works.

People can't simply take dopamine, because dopamine in the blood doesn't easily cross the blood-brain barrier, the protective layer of cells that controls what gets into the brain. Instead, NINDS explains, the main Parkinson's medicine is levodopa, which the brain converts into dopamine. It's almost always combined with a second medicine, carbidopa, which keeps the body from breaking levodopa down too early, so more of it reaches the brain.

Levodopa is usually swallowed as a pill, so it has a long trip before it can work. It has to leave the stomach, get absorbed into the blood from the upper part of the small intestine, and then cross into the brain. **Levodopa absorption** is the process by which levodopa taken by mouth passes from the gut into the bloodstream; in Parkinson's it can be delayed or uneven because of slow stomach emptying, constipation, and competition from protein in meals.

Each step can go wrong:

- **Slow stomach emptying.** Parkinson's can slow the stomach. A 2020 review by Pfeiffer and colleagues says delayed stomach emptying has been reported in a substantial fraction of people with Parkinson's and is linked to delayed levodopa levels in the blood and more "off" periods, times when symptoms come back because the medicine isn't working well.
- **Constipation and other gut problems.** A 2023 review by Leta and colleagues lists swallowing problems, slow stomach emptying, constipation, a stomach infection called *H. pylori*, bacterial overgrowth in the small intestine, and changes in gut microbes as possible barriers to levodopa reaching the blood.

- **Protein in meals.** Levodopa is carried across the gut wall by the same transport system that carries some amino acids (the building blocks of protein). A 2019 review by van Kessel and El Aidy notes that dietary amino acids can interfere with levodopa absorption, and NINDS notes that too much protein may limit how well people absorb carbidopa-levodopa.

This is why people with Parkinson's sometimes have unpredictable days when the medicine kicks in late or not at all. Their neurology team may adjust timing, treat the gut problems, or use forms of treatment that skip the gut entirely. One example is a levodopa-type medicine pumped slowly and steadily under the skin through a thin tube (Vyalev), which the FDA approved in October 2024 for motor fluctuations (swings between good and "off" periods) in adults with advanced Parkinson's. Those decisions belong to the care team; NINDS warns that people should never stop carbidopa-levodopa suddenly without talking with a doctor.

14.11 Alzheimer's Disease: Is the Gut Involved?

Now for the other big neurodegenerative disease. If Parkinson's is the disease of movement, Alzheimer's is the disease of memory and thinking.

Alzheimer's disease is a progressive brain disease that slowly destroys memory and thinking skills and, eventually, the ability to carry out everyday tasks; it is the most common cause of dementia in older adults. The Alzheimer's Association's 2026 Alzheimer's Disease Facts and Figures report estimates that about 7.4 million Americans aged 65 and older are living with Alzheimer's in 2026. Dementia means losing thinking, remembering, and reasoning abilities to the point that it interferes with daily life.

In 1906, Dr. Alois Alzheimer examined the brain of a woman who had died after memory loss, language problems, and unpredictable behavior. He found two kinds of abnormal deposits. Scientists now call them amyloid plaques and tau tangles, and the NIA says they're still considered main features of the disease.

Amyloid beta is a small protein fragment, cut from a larger protein in the brain, that can clump together into sticky plaques between neurons; these plaques are one of the main signs of Alzheimer's disease. Tau is a different protein that normally helps hold up the internal "railway tracks" of neurons; in Alzheimer's, it twists into tangles inside the cells. According to the NIA, these changes can begin a decade or more before symptoms appear, and damage often starts in memory areas such as the hippocampus.

Notice the pattern you saw in Parkinson's: a misfolding protein, a long silent period, and spread through connected regions. That has led researchers to ask whether gut microbes might nudge Alzheimer's too.

The human evidence is very early. In 2017, Vogt and colleagues compared stool samples from 25 people with Alzheimer's dementia and 25 people without it, matched for age and sex. The Alzheimer's group had less diverse gut bacteria and a different mix of bacterial groups, and some bacterial levels correlated with Alzheimer's markers in spinal fluid. That's interesting, but it's a single snapshot of 50 people.

It can't tell us which came first. People with dementia often eat differently, move less, take different medicines, and live in different settings, and any of those could change their gut microbes. In a 2024 review, Seo and Holtzman described research on gut microbes and Alzheimer's as "still in their infancy."

That hasn't stopped supplement marketing.

Hype Meter: "Probiotics prevent Alzheimer's"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. People with Alzheimer's have different gut bacteria in small studies, such as one comparing 25 patients with 25 matched controls, and mouse studies (summarized in a 2024 review by Seo and Holtzman) suggest microbes may affect amyloid buildup in mice. But a 2024 review describes the field as being in its infancy, and no large, long human trial has shown that any probiotic prevents Alzheimer's. The difference in microbes could be a result of the disease or of lifestyle, not a cause. **What would change the grade:** Large, long randomized trials in people, following them for years and showing fewer Alzheimer's diagnoses or slower decline with a specific product, could move it to Preliminary or higher. You'll learn how to read probiotic trials in Chapter 16.

For families

If a grandparent or parent has Parkinson's or Alzheimer's, you might be the one who notices changes first, like constipation, smell loss, low mood, or medicine that seems to wear off at certain times. These are worth mentioning to their doctor, because many of them are treatable. Try not to blame them for being slow, forgetful, or withdrawn; these are symptoms of the disease, and depression and anxiety in Parkinson's can be treated. Be cautious with supplements that promise to "protect the brain through the gut," and bring any product to the care team before trying it.

At the Bedside: Nanaji's Long Road to a Diagnosis

Meet the patient (fictional)

Nanaji is Riya's 72-year-old grandfather. Over the past two years his right hand has shaken at rest, his handwriting has gotten tiny, and he walks with small steps. Looking back, his family remembers other changes: constipation for many years, losing his sense of smell, and, according to Riya's grandmother, shouting and swinging his arms in his sleep as if fighting someone in a dream. Lately he seems quieter and more worried than he used to be.

What the doctor checks: A neurologist takes a careful history, including the non-movement symptoms that came first, and asks about medicines that can cause Parkinson-like symptoms. The physical exam looks for tremor at rest, rigidity, slowness, and balance problems. There's no single blood test for Parkinson's; the diagnosis is mainly based on the history and exam. In some cases, brain imaging helps rule out other causes. A sleep study can confirm REM sleep behavior disorder.

Connecting the signals: Nanaji has the classic movement symptoms caused by dopamine neuron loss. But his story also includes years of constipation, smell loss, and acting out dreams before the tremor. In the gut-first hypothesis, this order of events is what you'd predict if alpha-synuclein pathology began in body nerves and climbed through the brainstem's sleep circuits before reaching the substantia nigra. His doctor explains that this is an interesting fit, but no test can tell where his disease actually started.

Diagnosis: Parkinson's disease.

Why it happens: Dopamine-making neurons in his substantia nigra have been dying for years, probably along with neurons in his gut, smell system, and brainstem. Lewy bodies made of misfolded alpha-synuclein are found in damaged cells in most people with Parkinson's. Why the process started in him is unknown, as it is for most patients.

The mind-body side: Depression and anxiety are common in Parkinson's and can even appear before movement problems, according to NINDS. They are part of the disease, not a weakness, and they're treatable with therapy, medicine, or both. Nanaji's team screens for low mood, and his family learns that his quietness may be a symptom, not a sign that he's lost interest in them. Staying active and connected helps too; Riya plans a weekly cooking session with him and her grandmother.

Treatment today: The main treatment is carbidopa-levodopa, which usually works well for movement symptoms early in the disease but doesn't stop it from progressing. Because the medicine must be absorbed from the gut, his team also treats his constipation, for example with more fiber and fluids as NINDS suggests, and pays attention to meal timing and protein, which can affect levodopa absorption. Physical, occupational, and speech therapy help with walking, daily tasks, and voice. Exercise is encouraged. All medicine choices and changes are made with his neurologist.

What's new in research: In 2023, the Parkinson's Progression Markers Initiative reported results for a test that detects misfolded alpha-synuclein "seeds" in spinal fluid (Siderowf and colleagues, *Lancet Neurology*). Among 1,123 participants, the test was positive in 87.7% of people with Parkinson's and negative in 96.3% of healthy controls, and it found the seeds in 44 of 51 people with early warning signs (REM sleep behavior disorder or smell loss) who had not been diagnosed.

The test missed more often in some groups, though: it was positive in only 67.5% of people whose Parkinson's is linked to variants in a gene called *LRRK2*. Several of the study's authors work for Amprion, the company that developed the test.

In 2024, two expert groups used tests like this one to propose new "biological" definitions and stages of Parkinson's that start with finding misfolded alpha-synuclein rather than with symptoms (Simuni and colleagues; Höglinger and colleagues, both in *Lancet Neurology*). Both groups said their systems are for research only, and experts still debate them, partly because the test can be negative in some people with typical Parkinson's. **Evidence grade: Moderate** as a research tool for identifying Parkinson's biology; it is not a routine screening test for the general public, and it can't say where the disease began.

Your turn: reason through a variation

Nanaji's friend Mr. Okafor, also in his 70s, developed a tremor and slowness, but he never had constipation, smell loss, or dream-acting beforehand. His movement symptoms got worse fairly quickly, and only later did he develop constipation. Which proposed subtype does his story fit better, and what's the limit of that conclusion?

Answer: His story fits the brain-first subtype better: movement symptoms first, without REM sleep behavior disorder or gut problems beforehand, and gut problems later. But the subtypes are a hypothesis, symptoms like constipation have many causes, and memory of past symptoms can be fuzzy. No test available in routine care can show where his pathology started, so this is a teaching exercise, not a diagnosis.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: If you're constipated, you'll probably get Parkinson's.
Reality: People with constipation have about twice the odds of being diagnosed with Parkinson's later, but that's a relative comparison across huge groups. Constipation is very common and has many causes, Parkinson's mostly begins in older adults, and the great majority of constipated people never develop it.

Myth: The Braak hypothesis has been proven.
Reality: Braak's staging pattern is based on autopsies, which show where pathology is at death, not where it started. Mouse studies show gut-to-brain spread is possible, but human studies of vagus surgery are mixed, and a small fraction of patients don't fit the pattern. It's an influential hypothesis, not a settled fact.

Myth: Removing your appendix prevents Parkinson's.
Reality: One 2018 study found a lower risk, but another large study found a slightly higher risk, and two meta-analyses found no overall link. Appendix removal is not a prevention strategy.

Myth: Alzheimer's is caused by gut bacteria.
Reality: Small studies, such as one comparing 25 people with Alzheimer's to 25 without, found differences in gut bacteria. These are correlations, and the disease itself, along with diet, medicines, and activity, could change the microbes. The field is described by experts as still in its infancy.

Myth: "Prion-like" means Parkinson's is contagious.
Reality: "Prion-like spread" describes how misfolded alpha-synuclein may pass from one neuron to a connected neuron inside one person's nervous system. It does not mean you can catch Parkinson's from someone.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "New science proves Parkinson's starts in your gut. Heal your gut with our probiotic and protect your brain for life!"

Grade: Hype. The gut-first idea is a serious hypothesis (Moderate for some patients), supported by autopsy patterns, the constipation link, and mouse experiments. But nothing has "proven" it, human vagotomy and appendix studies are mixed, and no trial has shown that any probiotic prevents Parkinson's. The ad jumps from a contested hypothesis to a product. A careful version: "Some scientists think Parkinson's may begin in the gut in some people; researchers are still testing this idea."

2. Predict: Sam reads that Riya's grandfather has Parkinson's and asks whether Riya's Crohn's disease means she'll get it too. Using this chapter, what would you predict, and why?

There's no good reason to predict that Riya will get Parkinson's. Parkinson's mostly starts in people in their 60s or later, and most of the gut evidence in this chapter is about constipation as an early sign in older adults. Sam's question isn't silly, though: large studies of adults have found that people with inflammatory bowel disease, including Crohn's, are diagnosed with Parkinson's somewhat more often later in life (about 1.4 times as often in a 2024 pooled analysis of 7 cohort studies). That is a relative number for an uncommon disease, it comes from observational studies that can't show cause, and most people with Crohn's never develop Parkinson's. Having a grandparent with Parkinson's can matter a little in some families because genes play a part, but in most people the cause is unknown. If Riya is worried, the right step is to ask Dr. Alvarez, not to assume.

3. Explain: Why did cutting the vagus nerve block the spread of misfolded alpha-synuclein to the brain in the 2019 mouse study?

The misfolded protein was injected into the gut wall, and the vagus nerve is the main nerve line linking the gut to the brainstem's vagus nucleus. Prion-like spread passes from neuron to connected neuron, so the protein needs an unbroken chain of nerve cells to travel. Cutting the vagus removed that chain, so the protein couldn't reach the brainstem, and the dopamine neuron loss and behavior problems didn't happen.

4. Apply: Nanaji's levodopa seems to kick in late on days when he's very constipated and after big protein-heavy lunches. Use Section 14.10 to explain why.

Levodopa has to leave the stomach and be absorbed from the upper small intestine before it can reach the brain. Slow gut movement, which often goes along with constipation in Parkinson's, can delay that trip. Protein in meals breaks down into amino acids that compete with levodopa for the same transport system in the gut wall, so less levodopa gets absorbed, or it gets absorbed later. His care team, not his family, should decide on any changes to timing or diet.

5. Read the data. In 2017, Liu and colleagues used Swedish health registers to compare people who had a vagotomy with matched people who didn't. Here are their hazard ratios for later Parkinson's disease (1.0

means no difference; below 1.0 means lower risk). The numbers in parentheses are 95% confidence intervals: the range of values the data are compatible with.

Group compared with matched reference people	Hazard ratio (95% CI)
Any vagotomy (9,430 people)	0.96 (0.78 to 1.17)
Truncal vagotomy (3,445 people)	0.78 (0.55 to 1.09)
Truncal vagotomy at least 5 years before diagnosis	0.59 (0.37 to 0.93)

5. What does this data show, and what can't it show?

Overall, vagotomy wasn't linked to Parkinson's risk: 0.96 is close to 1.0, and the interval includes 1.0. For truncal vagotomy, the estimate is lower (0.78), but the interval still includes 1.0, so it could be chance. Only the subgroup with truncal vagotomy at least 5 years before diagnosis has an interval entirely below 1.0, which is consistent with the gut-first idea. But this is an observational study, so it can't prove that cutting the vagus caused the lower risk; people who had surgery may differ in other ways, and testing many subgroups raises the chance of a lucky result. A helpful follow-up would be a pooled analysis of all vagotomy studies, using the same definitions and long follow-up.

Exercises

Remember

1. What protein makes up most of a Lewy body?

Answer

Misfolded alpha-synuclein.

1. Name three prodromal symptoms that can come years before the movement symptoms of Parkinson's disease.

Answer

Any three of: constipation, loss of smell, REM sleep behavior disorder (acting out dreams), and depression or anxiety.

Understand

1. Explain why Parkinson's movement symptoms don't appear until the disease has been present for a long time.

Answer

The brain has a lot of reserve. According to NINDS, most people have already lost 60 to 80% or more of their dopamine neurons in the substantia nigra by the time movement symptoms appear, so the disease process runs quietly for years before it's visible.

1. In your own words, explain the difference between the two parts of the Braak hypothesis.

Answer

The first part is a staging pattern based on autopsies: Lewy pathology appears first in the brainstem vagus nucleus and a smell area, then climbs to higher brain regions. The second part is a guess about the origin: that in some people a trigger may enter through the gut and travel up the vagus nerve. The staging is a description; the gut origin is a hypothesis.

Apply

1. Using the MicroSim, run the gut-first and brain-first routes without cutting the vagus nerve. For each, record the model year when constipation, dream-acting, and movement symptoms begin. Then explain which symptom order each hypothesis predicts and why.
2. A news story says, "Study of 3,445 people shows cutting the vagus nerve protects against Parkinson's." Use the Swedish results in Your Gut Check question 5 to write a two-sentence correction.

Analyze

1. Compare the evidence from the 2019 mouse study (Kim and colleagues) and the 2017 Swedish vagotomy study (Liu and colleagues) using four of the six claim questions. Which one is better at showing cause, and which one tells you more about people?
2. The appendix studies disagree: one found lower risk, one found slightly higher risk, and two meta-analyses found no link. Analyze at least three reasons why large observational studies of the same question might reach different answers.

Evaluate

1. A classmate argues: "Since constipation comes 10 years before Parkinson's, the disease must start in the gut." Evaluate this argument. What does the timing support, and what other explanation fits the same data?
2. Judge which grade you would give the claim "Gut microbes cause Alzheimer's disease." Defend your grade using the Vogt 2017 study, the Seo and Holtzman 2024 review, and at least two of the six claim questions.

Create

1. Design a long-term study in people that could help decide between the gut-first and brain-first hypotheses. Describe who you would enroll, what you would measure (and when), and what result would support each hypothesis. Explain one ethical limit on what you could do.
2. Write a short, kind explanation (under 150 words) that Riya could give her younger cousin about why Nanaji had stomach problems before his shaking started, without scaring the cousin or overstating the science.

Key Takeaways

- Parkinson's disease is a neurodegenerative disease in which dopamine neurons in the substantia nigra die; most are gone before movement symptoms like tremor, rigidity, and slowness appear.
- Misfolded alpha-synuclein forms Lewy bodies, and it may spread from neuron to connected neuron (prion-like spread), which does not mean Parkinson's is contagious.
- Prodromal symptoms, including constipation, smell loss, REM sleep behavior disorder, and mood changes, can come years earlier. Constipation roughly doubles the odds of a later diagnosis, but most constipated people never develop Parkinson's.
- The Braak hypothesis proposes that pathology climbs from the brainstem and may begin in the gut; mouse studies show gut-to-brain spread is possible, but human vagotomy studies are mixed and appendix removal shows no overall link.
- Parkinson's may come in gut-first and brain-first subtypes that predict different symptom orders. This is an active, unresolved hypothesis.
- The gut also matters for treatment: slow stomach emptying, constipation, and protein can affect levodopa absorption.
- Alzheimer's disease involves amyloid beta plaques and tau tangles. Gut microbe differences have been found in small studies, but the research is very early, and claims that probiotics prevent Alzheimer's are hype.

You weighed a real scientific debate!



You just did what neurologists do: compared two competing ideas by the predictions they make and the evidence for each. Next, in Chapter 15, we'll turn from disease to everyday life and ask a question you face at every meal: can food change your mood?

Quiz: Parkinson's, Alzheimer's, and the Gut

Test your understanding of Chapter 14. Choose the best answer, then click **Show Answer** to check.

Question 1

What is the main cause of the movement symptoms of Parkinson's disease?

A. Loss of dopamine-making neurons in the substantia nigra

B. Amyloid beta plaques building up in the hippocampus

C. Damage to the muscles of the arms and legs

D. Too much serotonin made in the gut

Show Answer

The correct answer is **A**. Movement symptoms come mainly from the death of dopamine-making neurons in the substantia nigra; NINDS says most people have lost 60 to 80% or more of them by the time symptoms appear. Option B describes a hallmark of Alzheimer's disease, not Parkinson's.

Concept Tested: Dopamine Neuron Loss **Bloom's Level:** Remember

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Question 2

What is a Lewy body?

A. A bundle of vagus nerve fibers in the gut wall

B. A plaque of amyloid beta between neurons

C. An abnormal clump, made mostly of misfolded alpha-synuclein, inside a nerve cell

D. A group of gut bacteria found in people with Parkinson's

Show Answer

The correct answer is **C**. Lewy bodies are clumps of misfolded alpha-synuclein found inside damaged nerve cells in most people with Parkinson's. Option B mixes up Lewy bodies with the amyloid plaques of Alzheimer's disease, which form between neurons rather than inside them.

Concept Tested: Lewy Body **Bloom's Level:** Remember

Question 3

In Braak's 2003 staging system, where does Lewy pathology first appear in the brain?

A. In the outer cortex, then it moves down to the brainstem

B. In the substantia nigra only

C. In the hippocampus and memory areas

D. In the brainstem vagus nucleus and a smell-processing area

Show Answer

The correct answer is **D**. Braak's team reported that pathology first shows up in the dorsal motor nucleus of the vagus and an olfactory (smell) area, then climbs upward, reaching the substantia nigra in middle stages and the cortex last. Option A reverses the direction of the proposed spread.

Concept Tested: Braak Hypothesis **Bloom's Level:** Remember

Question 4

A 2016 meta-analysis found that people with constipation had an odds ratio of about 2.27 for a later Parkinson's diagnosis. What is the best interpretation?

A. Most people with constipation will develop Parkinson's disease.

B. Constipation is linked to about double the odds of a later diagnosis, but because Parkinson's is uncommon, most constipated people never develop it.

C. Constipation causes Parkinson's disease by damaging the substantia nigra.

D. Treating constipation prevents Parkinson's disease.

Show Answer

The correct answer is **B**. An odds ratio near 2 is a relative comparison between large groups; doubling a small chance still leaves a small chance. Option A is the most common misreading, and options C and D claim cause, which observational studies can't show.

Concept Tested: Constipation **Bloom's Level:** Understand

Question 5

What does "prion-like spread" mean in Parkinson's research?

A. Parkinson's can be caught from another person, like an infection.

B. Gut bacteria travel through the blood to the brain.

C. Misfolded alpha-synuclein may pass to connected neurons and make normal copies misfold, so damage moves along nerve pathways.

D. Dopamine leaks out of the brain into the gut.

Show Answer

The correct answer is **C**. Prion-like spread describes misfolding moving from neuron to connected neuron inside one person's nervous system, like falling dominoes. Option A is a common misunderstanding of the word "prion"; Parkinson's is not contagious between people.

Concept Tested: Prion-Like Spread **Bloom's Level:** Understand

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Question 6

How do the gut-first and brain-first subtypes differ in what they predict before diagnosis?

A. Gut-first predicts constipation and REM sleep behavior disorder years before movement symptoms; brain-first predicts movement symptoms earlier, with those problems usually absent before diagnosis.

B. Gut-first predicts memory loss first; brain-first predicts constipation first.

C. Both predict exactly the same order of symptoms.

D. Brain-first predicts that cutting the vagus nerve will prevent the disease.

Show Answer

The correct answer is **A**. In the gut-first idea, body nerves and brainstem sleep circuits are damaged before the dopamine system, so constipation and dream-acting come first. In the brain-first idea, the dopamine system is hit early. Option D gets it backward: the vagus route matters only in the gut-first idea.

Concept Tested: Gut-First Subtype **Bloom's Level:** Understand

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Question 7

A man has had trouble with his Parkinson's medicine kicking in late, especially after large, protein-heavy meals and on days when he is constipated. Which explanation fits the chapter best?

A. Protein and constipation destroy levodopa in the brain.

B. Levodopa can't cross the blood-brain barrier at all, so it never works.

C. His dopamine neurons grow back after meals.

D. Slow gut movement delays levodopa's trip to the small intestine, and amino acids from protein compete with it for absorption.

Show Answer

The correct answer is **D**. Levodopa is absorbed from the upper small intestine, so slow stomach emptying and constipation can delay it, and dietary amino acids share its transport system. Option B is wrong because levodopa does reach the brain, where it is converted into dopamine; it's dopamine itself that doesn't cross easily. Any changes should be made by his care team.

Concept Tested: Levodopa Absorption **Bloom's Level:** Apply

Question 8

A headline says: "Cutting the appendix slashes Parkinson's risk!" Based on the evidence in this chapter, what is the best response?

A. It's true, so people should consider having their appendix removed.

B. One 2018 study found lower risk, but a Danish study found slightly higher risk and two meta-analyses found no overall link, so the claim is not supported.

C. It's true only for people with constipation.

D. It's proven in mice, so it must be true in people.

Show Answer

The correct answer is **B**. The Killinger 2018 finding was not confirmed when studies were pooled: Lu 2020 found a relative risk of 1.02 and Chin 2025 found 1.01, both meaning no overall link. Option A turns a disputed association into a medical recommendation, which no evidence supports.

Concept Tested: Appendix and Parkinson's **Bloom's Level:** Apply

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Question 9

The Danish truncal vagotomy study found a hazard ratio of 0.53 (95% CI 0.28 to 0.99) for people followed more than 20 years, while the larger Swedish study found no overall link (hazard ratio 0.96). What is the most reasonable conclusion?

A. Cutting the vagus nerve is proven to prevent Parkinson's.

B. The vagus nerve has nothing to do with Parkinson's.

C. The human evidence is mixed: some subgroup results fit the gut-first idea, but they are imprecise and observational, so they can't prove cause.

D. The Swedish study must be wrong because it was larger.

Show Answer

The correct answer is **C**. The Danish result came from a subgroup, with a confidence interval that nearly reached 1.0, and the Swedish study found no overall effect. Both are observational, so differences between people who had surgery and those who didn't could explain the results. Option A overstates a weak, mixed signal.

Concept Tested: Truncal Vagotomy Studies **Bloom's Level:** Analyze

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Question 10

A 2017 study compared stool samples from 25 people with Alzheimer's and 25 matched people without it and found differences in gut bacteria. Which statement best analyzes what this study can show?

A. It shows a correlation in a small snapshot; the disease, diet, medicines, or activity could explain the bacterial differences.

B. It proves gut bacteria cause amyloid beta plaques in people.

C. It shows that probiotics prevent Alzheimer's.

D. It shows nothing at all because it studied people instead of mice.

Show Answer

The correct answer is **A**. This cross-sectional study of 50 people found an association, but it can't tell which came first, and people with dementia often differ in diet, activity, and medicines. Option B confuses correlation with cause; experts describe this research area as still in its infancy.

Concept Tested: Alzheimer's Disease **Bloom's Level:** Analyze

Chapter 15: Food and Mood

Summary

Headlines link food to mood almost every week, but most of those headlines come from studies that can only show that two things travel together, not that one causes the other. This chapter explains how researchers study whole dietary patterns, such as the Mediterranean diet and diets high in ultra-processed food, and what gut-brain pathways (fiber, fermented foods, and plant compounds called polyphenols) might connect food to the brain. You'll learn the difference between observational studies and randomized controlled trials, and how hidden factors like money, sleep, and existing low mood can create misleading links. Then you'll examine the real trials, including the SMILES trial, and see why diet may be a helpful add-on to depression care but never a replacement for it. Throughout, food is treated as nourishment, culture, and comfort, not as a moral test.

Concepts Covered

1. Dietary Pattern
2. Mediterranean Diet
3. Ultra-Processed Food
4. Dietary Fiber Gap
5. Fermented Food
6. Polyphenol
7. Nutritional Psychiatry
8. Observational Study
9. Randomized Controlled Trial
10. SMILES Trial
11. Dose-Response Relationship
12. Healthy User Bias
13. Mediator Variable
14. Food Insecurity
15. Eating Disorder Risk

Prerequisites

- Chapter 3: Meet the Microbiome for gut microbes, diversity, and correlation versus cause
- Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier for how microbes turn fiber into short-chain fatty acids
- Chapter 11: Anxiety, Depression, and the Gut for depression and two-way gut-brain links
- Chapter 13: Autism, ADHD, and the Gut for confounding variables

What's on your plate, and what's in the study?



You eat several times a day, so food-and-mood headlines feel personal. This chapter won't hand you a menu. Instead, it gives you the tools to read a nutrition study like a scientist, so you can tell a real finding from a link that hidden factors created. Let's check the evidence.

15.1 Chips and Sadness: Which Came First?

Sam was scrolling on the bus after cross-country practice when a headline stopped him: "Ultra-processed food linked to depression." He looked down at the bag of chips in his hand. He thought about the week before his last big test, when he felt low, slept badly, and lived on vending machine snacks because cooking felt like too much. So which came first? Did the snacks make him feel low, or did feeling low make him reach for the snacks? (Sam is a fictional student who appears throughout this book.)

He texted Riya, who was in her grandmother's kitchen, learning to make her family's dal and rotis. "Does that mean your grandma's cooking makes you happy?" he wrote. Riya laughed. "It definitely makes me happy. But I don't think that's what the study means."

Both of them are asking a sharp scientific question. A link between food and mood could mean food affects mood, or mood affects food, or something else, like money, time, or sleep, affects both. This chapter is about telling those apart. By the end, you'll be able to read Sam's headline and know exactly what it can and can't tell him.

15.2 Thinking in Patterns, Not Single Foods

Start with an everyday comparison. If you wanted to know whether a soccer team is good, you wouldn't judge it by one player or one game. You'd look at how the whole team plays over a season. Nutrition researchers have learned to think the same way about food.

People don't eat single nutrients in isolation. They eat meals, made of many foods, in combinations that repeat over weeks and years. A **dietary pattern** is the overall combination of foods and drinks a person usually eats over time, studied as a whole instead of one food or nutrient at a time. Studying patterns helps because foods come in bundles. Someone who eats a lot of beans probably also eats differently in other ways, so looking at beans alone could be misleading.

The field that studies these links has a name. **Nutritional psychiatry** is the area of research that studies how diet and nutrition relate to mental health, including whether changing diet can help prevent or treat conditions like depression and anxiety. It's a young field. A 2020 analysis in the *BMJ* by Firth and colleagues concluded that poor nutrition may contribute to low mood, but that the evidence is still developing and many questions remain open.

Before we go further, one important note about how this book talks about food. Every food can be part of a person's life, and food is also family, culture, celebration, and comfort. When researchers compare "diet quality," they are measuring patterns across large groups, not judging anyone's plate. This chapter never sorts foods into "good" and "bad," and it never talks about body size. Mood is the topic, and the question is always "what does the evidence show?"

Patterns beat single foods



When a post claims one food or one supplement will change your mood, remember that the research mostly studies whole patterns over weeks or years. A single food is one player, not the whole team.

15.3 Four Ingredients Researchers Watch

Researchers often describe dietary patterns using a few big features. Here are the ones that connect most directly to the gut-brain axis.

The Mediterranean diet

The **Mediterranean diet** is a dietary pattern based on the traditional eating habits of countries around the Mediterranean Sea, rich in vegetables, fruits, whole grains, legumes (beans and lentils), nuts, olive oil, and fish, with fewer highly processed foods. There isn't one official version. In the SMILES trial (Section 15.6), for example, dietitians encouraged foods from 12 groups, including whole grains, vegetables, fruit, legumes, nuts, fish, and olive oil, with fewer refined cereals, fried and fast foods, processed meats, and sugary drinks.

The word "Mediterranean" can sound like it's about one culture's cuisine. It isn't really. Many food traditions, including Indian, Mexican, Ethiopian, and East Asian home cooking, are built on legumes, vegetables, whole grains, and spices. Riya's grandmother's dal, made from lentils, is packed with the same kinds of ingredients researchers count in Mediterranean-style scores.

Ultra-processed food

The **ultra-processed food** label comes from the NOVA classification system, developed in 2009, which groups foods by how much industrial processing they go through. Ultra-processed foods are industrial formulations made mostly from substances extracted or derived from foods, often with additives such as flavors, colors, or

emulsifiers that you wouldn't use in a home kitchen. Examples include many packaged snacks, sweetened drinks, and ready-to-eat products. The category is about processing, not about any single nutrient, and many people rely on these foods because they're affordable, quick, and shelf-stable.

The fiber gap

You met fiber in Chapter 6: the parts of plant foods that your own enzymes can't digest, which your gut microbes ferment into short-chain fatty acids. The **dietary fiber gap** is the difference between how much fiber people actually eat and how much dietary guidelines suggest.

Measure	Amount	Source
Average US intake	About 16 grams a day (16.2 g, 2009 to 2010 national survey)	Quagliani and Felt-Gunderson 2017
Suggested for girls 14 to 18	About 25 grams a day	Dietary Guidelines for Americans, 2020 to 2025
Suggested for boys 14 to 18	About 31 grams a day	Dietary Guidelines for Americans, 2020 to 2025
Share not meeting the goal	More than 90% of women and 97% of men	Dietary Guidelines for Americans, 2020 to 2025

The newest federal guidelines, the *Dietary Guidelines for Americans, 2025 to 2030*, don't give a gram target. Instead, a "Gut Health" box says highly processed foods can disrupt the balance of the microbiome, while vegetables, fruits, fermented foods, and high-fiber foods support a diverse microbiome, "which may be beneficial for health." These numbers describe the whole population. They aren't a personal target, and people with some gut conditions, including some people with Crohn's disease like Riya, get different fiber advice from their care team.

Fermented foods and polyphenols

Fermented food is food made by letting microbes such as bacteria or yeasts transform it, as in yogurt, kefir, kimchi, sauerkraut, miso, and many traditional foods like idli and dosa batter. In a 2021 Stanford study, Wastyk and colleagues randomly assigned 36 healthy adults (18 per group) to eat more fermented foods or more fiber for 17 weeks. The fermented-food group had steadily rising gut microbe diversity and lower levels of several inflammation markers in the blood. That's a randomized experiment, which is a strength, but it was small, short, done in healthy adults, and it measured microbes and immune markers, **not mood**.

A **polyphenol** is one of a large family of natural chemical compounds made by plants, found in foods such as berries, grapes, onions, tea, and spices like turmeric, that may affect the body partly through the gut microbes

that break them down. According to a 2021 review by Chiu and colleagues, only about 5 to 10% of the polyphenols people eat are absorbed in the small intestine; roughly 90% reach the large intestine, where gut microbes break them into smaller compounds. That's why scientists think polyphenols and microbes may work as a team. Most of the brain-related evidence for polyphenols, though, comes from lab and animal studies.

The table below summarizes the four features and how they might connect to the gut-brain axis.

Pattern feature	Possible gut-brain connection	Strength of evidence for mood
Mediterranean-style eating	More fiber, polyphenols, and olive oil, nuts, and fish; less inflammation	A few small trials (Section 15.6)
Ultra-processed food	Less fiber; additives might affect microbes	Associations only (Section 15.5)
Fiber	Microbes make short-chain fatty acids	Mostly animal and indirect human evidence
Fermented foods and polyphenols	Change microbe diversity and inflammation markers	Microbe and immune changes in people; mood not tested

15.4 Two Ways to Study Food and Mood

Now for the most important tool in the chapter. Suppose you want to know whether eating more vegetables improves mood. There are two basic ways to find out.

Way 1: Watch. Ask thousands of people what they eat and how they feel, then see whether the two go together. An **observational study** is a study in which researchers measure what people already do (such as what they eat) and their health, without assigning anyone to change anything, and then look for links. Observational studies can be huge, cheap, and long, so they're great for spotting patterns.

Way 2: Change one thing on purpose. Take a group of people and use chance, like a coin flip, to decide who gets diet coaching and who doesn't. A **randomized controlled trial** (RCT) is an experiment in which participants are randomly assigned to receive a treatment or a comparison condition, so the groups start out alike on average, and any difference at the end can be credited to the treatment. Randomization is powerful because, on average, it balances everything, including things researchers didn't think to measure. In a small trial, chance can still leave the groups somewhat different.

This matters a lot in nutrition, because in an observational study, people who eat differently also tend to live differently. Three traps show up again and again.

Trap 1: Confounding. A confounding variable is a hidden third factor that affects both the thing you think is the cause and the outcome. Money is a classic example: families with more money can usually afford more fresh food **and** have less financial stress, which affects mood. Diet and mood would be linked even if food itself did nothing.

Trap 2: Reverse causation. Depression often changes appetite, energy, and motivation to cook. If low mood makes people eat more convenience foods, diet and mood are linked, but the arrow points from mood to food. The 2022 review of ultra-processed food by Lane and colleagues noted that the link appeared to run in both directions, though most of its studies were snapshots that can't settle which way.

Trap 3: Healthy user bias. Healthy user bias is a distortion in observational studies that happens because people who choose one health-related behavior, such as following dietary advice, often also have many other health-related habits and advantages (more sleep, more exercise, regular checkups, less smoking), which make that behavior look more beneficial than it really is.

Who chose the food?



My favorite question for any food study: who decided what people ate? If people chose for themselves, hidden factors can sneak in. If a coin flip decided, those hidden factors get spread evenly between the groups.

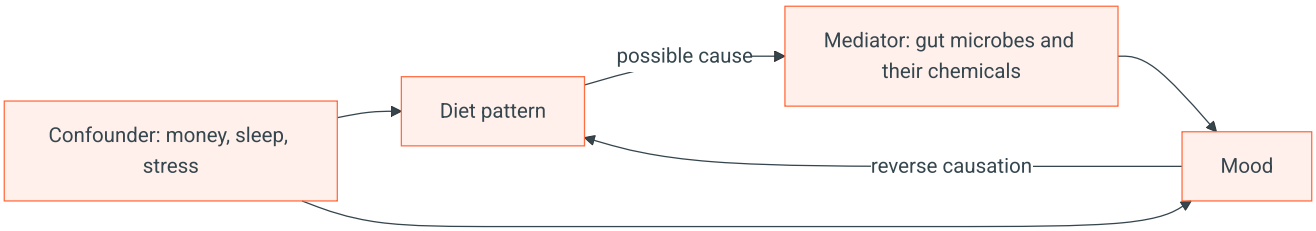
Two more tools for reading diet studies

Observational researchers aren't helpless. They use clues that make a cause more or less believable.

A **dose-response relationship** is a pattern in which more of an exposure goes with a steadily larger effect, for example, a little more of a food linked with a little more of an outcome, and a lot more linked with a lot more. A dose-response pattern makes a causal story more believable, because it's what you'd expect if the exposure really mattered. But it isn't proof. A confounder that also comes in "doses," like income, can create the same smooth pattern.

A **mediator variable** is a factor that lies on the causal path between a cause and an outcome and helps explain **how** the cause produces its effect. For example, if fiber improved mood, gut microbes and the short-chain fatty acids they make could be mediators: fiber changes microbes, microbes make short-chain fatty acids, and those chemicals affect the brain. Notice the difference from a confounder. A confounder sits **outside** the path and affects both ends; a mediator sits **inside** the path, carrying the effect along. Mixing them up leads to wrong conclusions: if you "adjust away" a mediator, you can accidentally hide a real effect.

Here's a simple flowchart of the three ways a diet-mood link can arise. Each arrow means "affects."



15.5 Ultra-Processed Food and Mood: What the Studies Show

Let's return to Sam's headline. What do the studies actually show?

In 2022, Lane and colleagues combined 17 observational studies with 385,541 people. Most (15) were cross-sectional, meaning they measured diet and mood at one moment, and 2 were prospective, meaning they measured diet first and followed people forward. People who ate more ultra-processed food had higher odds of depression symptoms (an odds ratio of 1.44) and anxiety symptoms (1.48). In the two prospective studies, higher intake was linked to a 22% higher risk of later depression (a hazard ratio of 1.22).

In 2024, a larger "umbrella review" in the *BMJ* by the same research group pulled together 45 pooled analyses covering nearly 10 million people. Ultra-processed food was linked to 32 of 45 health outcomes. Under their rules, the links with anxiety and common mental disorders counted as "convincing" evidence of an **association**. But when the team graded the **quality** of the evidence with a standard system called GRADE, those same mental health links were rated "low" quality. Across all 45 analyses, only 4 were rated moderate quality; 22 were low and 19 were very low.

How can evidence be "convincing" and "low quality" at once? "Convincing" is a statistical label: the link is backed by large numbers of people, is consistent across studies, and is very unlikely to be a statistical fluke. It doesn't mean the effect is big. "Low quality" means the studies' designs (mostly observational, often snapshots) can't rule out confounding or reverse causation. A link can be very real and still not tell you what causes what.

Hype Meter: "Eating lots of ultra-processed food is linked to depression"

Strong	**Moderate**	Preliminary	Hype

Verdict: Moderate. (The stronger claim that ultra-processed food *causes* depression is not shown.) Large pooled analyses of observational studies (17 studies and 385,541 people in 2022; nearly 10 million people across a 2024 umbrella review) consistently link more ultra-processed food with more depression and anxiety symptoms. But most studies are snapshots, the evidence quality was rated low, money and stress can affect both diet and mood, and low mood can change what people eat. "Linked to" is accurate; "causes" is not shown. **What would change the grade:** Randomized trials that change ultra-processed food intake while keeping other things equal, and that measure mood over months, could upgrade the causal claim. Long prospective studies that carefully account for income, sleep, and earlier mood would also help.

15.6 Testing Diet in Trials: SMILES and Beyond

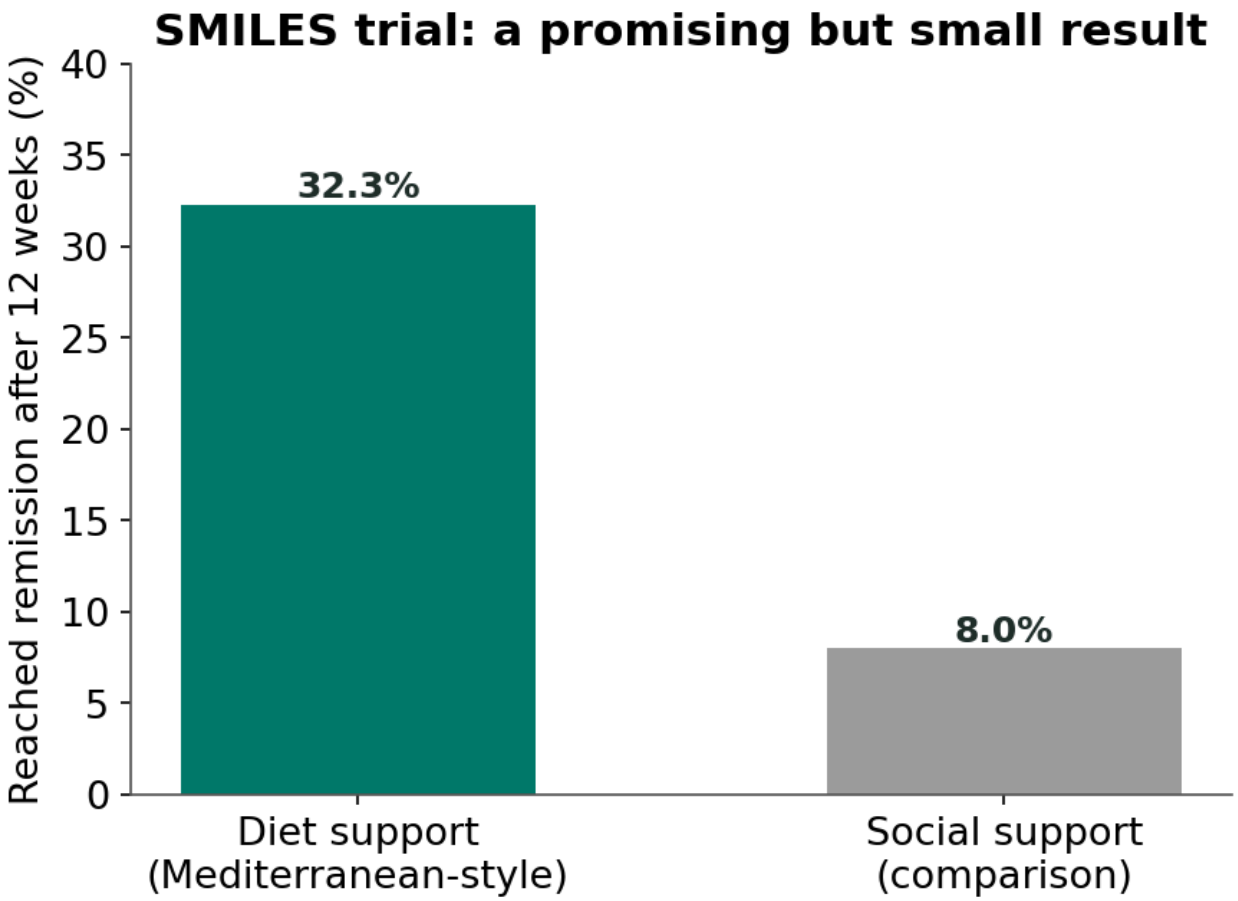
To get closer to cause, researchers need randomized trials. There aren't many, and they're hard to run, because you can't hide from people what they're eating.

The SMILES trial

The **SMILES trial** (Supporting the Modification of lifestyle In Lowered Emotional States) was a 12-week randomized controlled trial, published in 2017 by Felice Jacka and colleagues in Australia, that tested whether dietitian support toward a Mediterranean-style diet improved symptoms in adults with moderate to severe depression.

The researchers enrolled 67 adults with moderate to severe depression and randomly assigned them to one of two groups. One group (33 people) had seven sessions with a clinical dietitian, who helped them shift toward the 12 food groups described in Section 15.3. The comparison group (34 people) got "social support": friendly sessions with a trained person, on the same schedule and for the same length of time, but with no diet advice. Most participants (55 of 67) were already getting therapy, medication, or both, so diet support was an **add-on**, not a replacement for treatment.

The results: among people who had complete data at 12 weeks (31 in the diet group and 25 in the social support group), depression scores improved more in the diet group. Remission, meaning symptoms low enough to count as no longer depressed on the rating scale, happened in **32.3%** of the diet group (10 of 31) versus **8.0%** of the social support group (2 of 25).



Source: Jacka et al. 2017, BMC Medicine. 67 adults were randomized; percentages are among the 56 who finished (31 and 25), and participants knew which group they were in.

How to read a gut-brain claim: the SMILES trial

Question	This study
Mouse or human?	Human: 67 adults with moderate to severe depression.
Correlation or cause?	Cause, in principle: people were randomly assigned. But participants knew which group they were in (only the people rating their depression were blinded), which can affect results.
How many?	Small: 67 enrolled, and only 56 had complete 12-week data (31 vs 25).
How long?	12 weeks. It can't show whether benefits last.
Who paid for it?	Mainly the National Health and Medical Research Council of Australia. Woolworths (a supermarket chain) provided food vouchers, other companies donated small items, and Meat and Livestock Australia funded some blood tests; the paper says sponsors had no role in the design or analysis. Several authors reported other industry and foundation funding.
Is something being sold?	No specific product. In a later paper (2022), the lead author disclosed that she has written two books for commercial publication and personally believes diet quality matters for mental health.

The conclusion: SMILES is a promising, carefully designed early trial, and its result is striking. But it's small, short, not fully blinded, and limited to adults who mostly had other treatment too. One trial, no matter how exciting, needs to be repeated before anyone should rely on it.

Other trials

Three other studies help put SMILES in context.

- **HELFIMED (2019).** Parletta and colleagues recruited 152 adults with self-reported depression. One group got food hampers and Mediterranean-style cooking workshops for 3 months, plus fish oil supplements for 6 months; the other attended social groups. The diet group had a greater drop in depression at 3 months. But only 95 people completed the 3-month check, and because the diet came with fish oil, you can't credit the result to food alone.
- **Firth and colleagues' meta-analysis (2019).** This combined 16 randomized trials with 45,826 participants, mostly people without diagnosed depression. Diet-improvement programs reduced depressive symptoms

by a small amount (an effect size of about 0.16, where 0.2 is usually called "small") but did not significantly reduce anxiety.

- **PREDIMED (2013).** In a large Spanish heart-health trial of 3,923 older adults (ages 55 to 80) at high risk of heart disease, a Mediterranean diet with extra nuts did **not** significantly lower the overall risk of new depression compared with a low-fat diet. A benefit showed up only in the subgroup with type 2 diabetes, an exploratory finding in older adults, not teens. (PREDIMED's main 2013 heart-disease paper was retracted and republished in 2018 after problems were found with how some participants were randomized. This depression analysis comes from the same trial, so treat its subgroup result with extra caution.)

Hype Meter: "Eating a Mediterranean diet treats depression"

Strong	Moderate	**Preliminary**	Hype

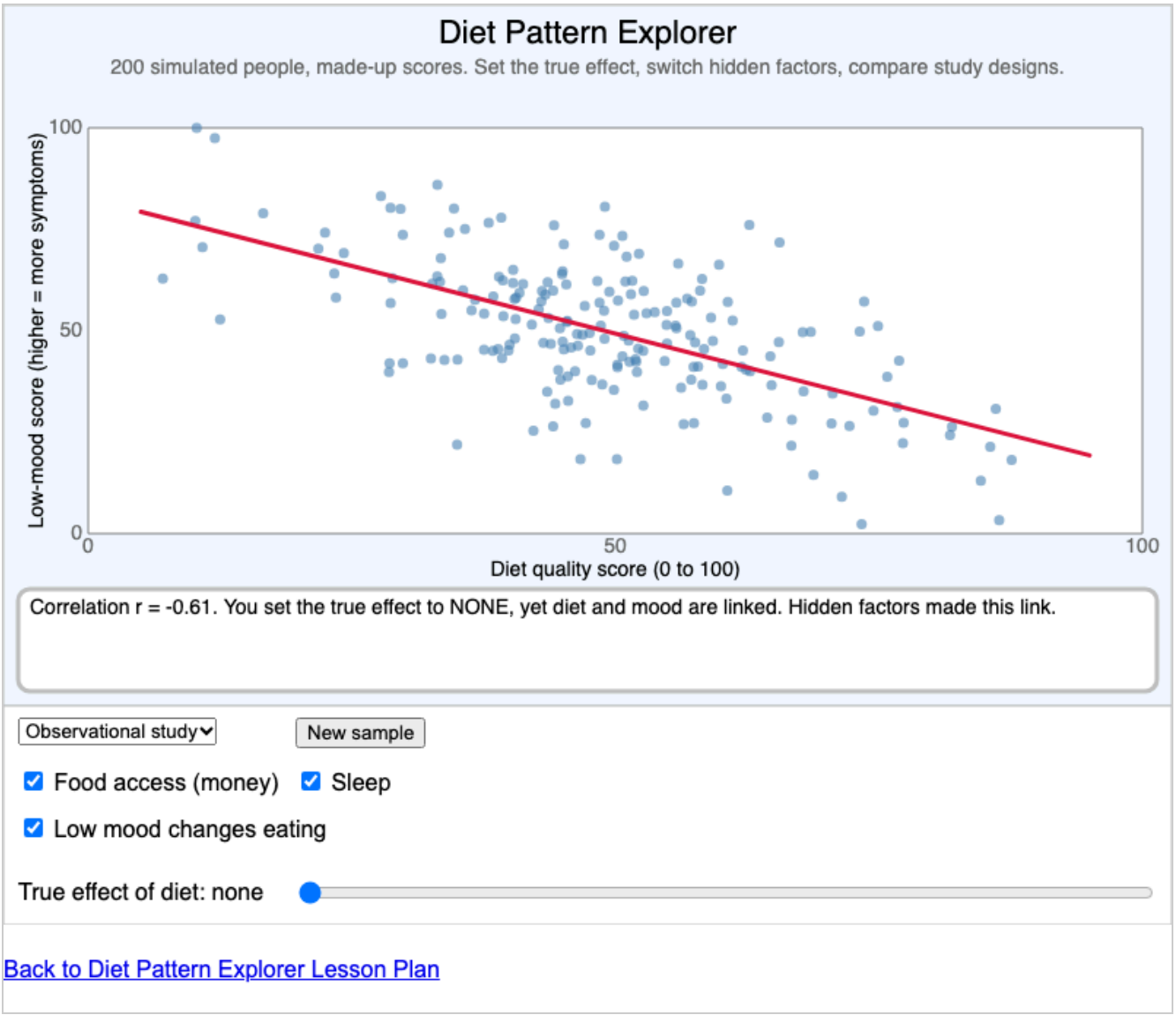
Verdict: Preliminary. A few small randomized trials, including SMILES (67 adults, 12 weeks, remission 32.3% vs 8.0%) and HELFIMED (152 adults, diet plus fish oil), found improvements when diet support was added to usual care. A meta-analysis of 16 trials found a small effect on depressive symptoms, and the large PREDIMED trial found no significant overall effect on new depression. The trials were small or short, participants knew their group, and diet was an add-on, not a replacement for therapy or medicine. **What would change the grade:** Several larger, longer trials, in different countries and age groups including teens, with careful comparison groups and consistent results, could move it to Moderate. A careful version of the claim: "Adding dietitian support may help some adults with depression, alongside usual treatment."

See the Hype Meter page for how the four grades are defined.

15.7 The Diet Pattern Explorer

The best way to understand confounding is to watch it fool you. In the MicroSim below, you'll study a population of simulated people. You get to decide two things that real scientists never know for sure: how much diet **truly** affects mood in this made-up world, and which hidden factors are present. "Food access" stands for money and nearby stores, "sleep" for how well people sleep, and "low mood changes eating" switches on reverse causation. The scores are made-up numbers from 0 to 100.

Diagram: Diet Pattern Explorer



Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch15-diet-pattern-explorer/main.html

Open the Diet Pattern Explorer fullscreen

MicroSim specification: Diet Pattern Explorer

Type: microsim **sim-id:** ch15-diet-pattern-explorer
Library: p5.js
Status: Implemented
Bloom Level: Analyze
Bloom Verb: distinguish
Learning Objective: The learner will distinguish association from causation in nutrition research by showing that hidden factors can create a diet-mood correlation even when diet has no true effect, and that random assignment removes that confounding.

Canvas: 480 px drawing area plus 150 px controls (iframe 632 px); responsive to about 380 px wide.

Controls: Study design select (Observational study; Randomized trial); New sample button; checkboxes for Food access (money), Sleep, Low mood changes eating; True effect of diet slider (none to strong, 0 to 0.5 in steps of 0.1).

Rules: 200 simulated people. Hidden factors are standard normal values (zero when switched off). Diet = 0.6 x food access + 0.4 x sleep - 0.6 x earlier low mood + noise. In a trial, a coin flip adds 1.5 to diet for the coaching group regardless of hidden factors. Low-mood score = -(true effect) x diet - 0.5 x food access - 0.6 x sleep + 0.8 x earlier low mood + noise. Scores are shown on a 0 to 100 scale.

Feedback: Observational mode shows a scatter plot, best-fit line, and correlation r; trial mode shows the two randomized groups with means and the difference. A message compares the result with the true effect the learner set.

Provenance: Concepts from Section 15.4 (confounding, reverse causation, healthy user bias) and Section 15.6 (randomized trials such as SMILES). All people and numbers are simulated.

Start in **Observational study** mode with the true effect set to **none** and all three hidden factors switched on. Look at the scatter plot: people with higher diet scores have lower low-mood scores, and the correlation is clearly negative. But you set the true effect to zero! Every bit of that link comes from hidden factors. Now switch the hidden factors off one at a time and watch the correlation shrink. Which one creates the most fake link?

Next, switch to **Randomized trial** mode without changing anything else. A coin flip now decides who gets diet coaching. With the true effect at none, the two groups end up with nearly the same average low-mood score, even with all the hidden factors still on. Raise the true effect and watch a real difference appear. Press **New sample** a few times: the trial's answer wobbles by chance from sample to sample, which is why one small trial isn't enough.

What this model leaves out

- The people, scores, and effect sizes are made up. Real diets and moods can't be summed up in one number each.
- Real confounders are far more numerous and tangled (culture, family, school stress, medicines, illness, physical activity), and many can't be measured.
- The model's "trial" is perfect: everyone follows the diet coaching and nobody drops out. Real trials like SMILES lose participants, and people know their group.
- It shows only a direct diet-to-mood effect; it leaves out mediators like gut microbes and the possibility that diet affects different people differently.
- The model can't show harms. In real life, restrictive diets can cause problems, which a mood score alone wouldn't capture.

15.8 Healthy Eating Isn't Equally Easy for Everyone

Now go back to the "food access" switch in the sim. It stands for something real.

Food insecurity is the condition of not having reliable access to enough food for an active, healthy life, because of limited money or other resources; households that are food insecure are uncertain of having, or unable to get, enough food for all their members. According to the US Department of Agriculture, in 2024, 13.7% of US households (about 18.3 million households, including 47.9 million people) were food insecure at some time during the year. Among households with children, the rate was 18.4%.

Food insecurity matters for food-and-mood research in two ways. First, it's a powerful confounder. Worrying about money and food is stressful, and stress affects mood, so studies that don't account for it can blame (or credit) the food instead of the circumstances. Second, it reminds us that "just eat better" isn't fair advice. Fresh produce, time to cook, a kitchen, and nearby grocery stores aren't available to everyone. Shelf-stable, quick foods are often the most practical option for busy families, and there's nothing shameful about that.

For families

If someone in your family is struggling with low mood, meals can be a gentle way to support them without pressure: cooking together, eating together, or simply making sure food is available when energy is low. Avoid commenting on what or how much they eat, and never frame food as a test of willpower. If money for food is tight, school meal programs, food banks, and federal programs such as SNAP exist for exactly this purpose, and a school counselor or social worker can help you find them. Diet is never a substitute for mental health care; if someone seems depressed, help them talk to a doctor.

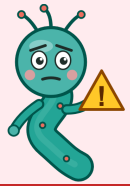
15.9 When Food Changes Become Risky: Eating Disorder Risk

There's one more reason this book is careful about food advice. Diet messages, even well-meaning ones, can push some people toward restrictive eating.

Eating disorder risk refers to the chance of developing an eating disorder, a serious illness marked by severe disturbances in eating behaviors, thoughts, and feelings about food; strict food rules, cutting out whole food groups, or intense focus on eating "perfectly" can be warning signs. The National Institute of Mental Health (NIMH) describes eating disorders as serious and sometimes life-threatening illnesses, and it stresses that they can be treated successfully and that early detection and treatment are important for recovery.

This connects directly to the chapter. A headline that says "this food causes depression" can sound like a rule: never eat it. A teen who is already anxious might start cutting out more and more foods, hoping to feel better. That's the opposite of what the evidence supports. The trials in this chapter **added** variety and support; none of them tested cutting out food groups to improve mood. People with gut conditions face extra risk here, because they sometimes need medically supervised diets (like celiac disease's gluten-free diet), and the line between "medically needed" and "self-imposed" restriction can blur.

Don't turn a headline into a food rule



A study that links a food pattern with mood across thousands of people is not a rule for your plate. If you notice yourself making stricter and stricter food rules, or feeling guilty after eating, that's worth talking about with a doctor or counselor.

If you're going through this

If you're dealing with low mood, a gut condition, or both, you might feel pressure to "eat perfectly" to fix how you feel. You don't have to. Food can be one gentle part of feeling better, but it works best alongside the care that helps most, like therapy, medicine when needed, sleep, and people you trust. If you have a gut condition, ask your care team before changing your diet, and ask for a referral to a registered dietitian if food feels confusing or stressful. If you are ever in crisis, you can call or text **988** to reach the 988 Suicide & Crisis Lifeline in the US.

At the Bedside: Food as One Part of a Plan

Meet the patient (fictional)

Jordan is 17 and a senior. For the past two months Jordan has felt flat and tired, has stopped enjoying soccer, and has trouble sleeping. Meals have become irregular, mostly snacks grabbed between classes, because cooking or even deciding what to eat feels exhausting. Jordan's parent saw a video saying "fix your gut, fix your depression" and asks the family doctor whether Jordan should start a strict "gut-healing" diet.

What the doctor checks: The doctor asks about mood, sleep, appetite, energy, school, friends, and any thoughts of self-harm, and uses a standard depression questionnaire. A physical exam and, if needed, blood tests look for medical causes of tiredness, such as thyroid problems or anemia. The doctor also asks gently about eating: skipped meals, food rules, worry about food, and whether there's always enough food at home.

Connecting the signals: Jordan's low mood, poor sleep, and loss of interest came first; the change in eating looks like part of the depression, not its cause. This is the reverse causation arrow from Section 15.4. At the same time, irregular eating and poor sleep may make Jordan feel worse, so the two can feed each other in a loop.

Diagnosis: Depression (major depressive episode).

Why it happens: Depression has many causes, including genes, stress, sleep, and life events. Diet may be one small piece in some people, possibly through pathways involving gut microbes and inflammation, but the evidence for that in teens is limited. What's clear is that depression itself often changes appetite and eating.

The mind-body side: The doctor explains that food is nourishment and comfort, not a test Jordan is failing. A strict elimination diet isn't recommended; there's no solid evidence it treats depression, and restrictive eating can raise the risk of an eating disorder in a teen who is already struggling. The family also learns that blaming Jordan's snacks for the depression would add guilt to an illness Jordan didn't choose.

Treatment today: Depression in teens is usually treated with talk therapy, and sometimes with medicine prescribed and monitored by a doctor. The doctor refers Jordan to a therapist and also to a registered dietitian, whose job is to help Jordan eat regularly and enough, adding easy, enjoyable foods (including foods from the family's own traditions) rather than cutting things out. Sleep and gentle activity are part of the plan too. Every change is made with the care team.

What's new in research: In 2022, the AMMEND trial by Bayes and colleagues in Australia randomly assigned young men aged 18 to 25 with moderate to severe depression to 12 weeks of Mediterranean diet support or to "befriending" sessions; 72 completed the study. On a depression questionnaire the men filled out themselves (the BDI-II), the diet group's scores dropped about 14 points more than the befriending group's, a very large difference. **Evidence grade: Preliminary.** Treat that size with caution. The trial was small and short, it was open-label (participants knew their group) while the main outcome was the men's own rating of their mood, and it included only young men. Larger trials, ideally with depression rated by people who don't know each participant's group, are needed to see whether an effect this big holds up, and it doesn't yet tell us what would happen in teens or other groups.

Your turn: reason through a variation

Six months later, Jordan's mood has improved a lot with therapy, and Jordan is eating more regular meals. Jordan's parent says, "See, it was the food all along." How would you reason about this?

Answer: Several things changed at once: therapy, regular meals, better sleep, and time. Depression can also improve on its own over months. With everything changing together, there's no way to tell which part helped most, which is exactly why researchers use randomized trials. It's fine to keep the routines that help, but this one story can't show that food caused the improvement.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: One superfood can fix your mood.
Reality: Research studies whole dietary patterns over weeks or years, and even for patterns, the trials are few and small, and pooled effects are small. No single food has been shown to treat depression.

Myth: A big observational study proves that a food causes depression.
Reality: Observational studies show links, which can come from confounders like money and sleep, from healthy user bias, or from low mood changing what people eat. Only randomized trials can test cause directly, and those are still few and small.

Myth: Cutting out food groups is a good way to improve mood.
Reality: The diet trials in this chapter added variety and support; none tested cutting out food groups for mood. Unneeded restriction can lead to missing nutrients and can raise eating disorder risk. Medically needed diets should be guided by a care team.

Myth: Healthy eating is equally easy for everyone.
Reality: In 2024, 13.7% of US households were food insecure at some point. Money, time, cooking space, and nearby stores shape what people can eat, which is also why these factors confound diet studies.

Myth: Diet can replace therapy or medicine for depression.
Reality: In SMILES, most participants were already in therapy or on medication, and diet support was an add-on. Depression should be treated with a care team.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Depression is caused by processed food. Cut it out completely and you won't need antidepressants!"

Grade: Hype. Large observational studies link ultra-processed food with more depression symptoms (a Moderate association), but they can't show cause, and the link may run in both directions. No trial has shown that cutting out processed food treats depression, and the trials that helped added diet support **on top of** usual treatment. Telling someone to stop medicine on the basis of a diet claim could cause real harm. A careful version: "Diets high in ultra-processed food are linked to depression symptoms, but we don't yet know if changing them helps."

2. Predict: Sam notices that on test weeks he eats more vending machine snacks and feels more anxious. Predict what a researcher would see if they surveyed thousands of students like Sam once, and explain why that wouldn't show the snacks caused the anxiety.

The survey would probably find that students who eat more packaged snacks report more anxiety. But test stress could cause both: stressed students sleep less, have less time to eat regular meals, and feel more anxious. Anxiety could also change eating (reverse causation). A one-time survey can't tell which came first or rule out the shared cause, so it shows a link, not a cause.

3. Explain: In the Diet Pattern Explorer, why does a strong correlation appear in observational mode even when the true effect of diet is set to none?

The hidden factors affect both diet and mood. In the sim, more food access and better sleep raise diet scores **and** lower low-mood scores, and earlier low mood lowers diet scores while raising low-mood scores. So people line up along a diagonal even though diet itself does nothing. That's confounding (food access, sleep) plus reverse causation (low mood changes eating).

4. Apply: A study finds that teens who eat the most fermented foods have the best mood scores, and the link gets stronger the more fermented food they eat. A classmate says the dose-response pattern proves fermented foods improve mood. How do you respond?

A dose-response pattern makes a causal story more believable, but it isn't proof. A confounder that also comes in degrees, such as family income or cultural food traditions that come with strong family support, could produce the same smooth pattern. Healthy user bias could also play a role. A randomized trial that assigns fermented foods and measures mood would be needed; the 2021 Stanford fermented-food trial measured microbes and inflammation, not mood.

5. Read the data. In the SMILES trial (Jacka et al. 2017), adults with moderate to severe depression were randomly assigned to dietitian support or social support for 12 weeks. Here are the remission results among people with complete 12-week data:

Group	People with 12-week data	Reached remission	Percentage
Diet support	31	10	32.3%
Social support	25	2	8.0%

5. What does this data show, and what can't it show?

It shows that, in this trial, remission was about four times as common with diet support as with social support (32.3% vs 8.0%), and because people were randomized, the groups started out alike on average. But the numbers are tiny: a difference of a few people would change the percentages a lot, and 11 of the 67 enrolled people are missing from this table. Participants knew their group, the trial lasted only 12 weeks, and most people were also in therapy or on medication, so it can't show that diet alone treats depression or that the benefit lasts. A larger, longer trial in several places, including teens, would help.

Exercises

Remember

1. What is the difference between an observational study and a randomized controlled trial?

Answer

In an observational study, researchers measure what people already do and look for links, without assigning anything. In a randomized controlled trial, chance decides who gets the treatment or comparison, so the groups start out alike on average.

1. In the SMILES trial, what were the remission rates in the diet support and social support groups?

Answer

32.3% (10 of 31) in the diet support group and 8.0% (2 of 25) in the social support group, among people with complete 12-week data.

Understand

1. Explain the difference between a confounder and a mediator, using fiber, gut microbes, mood, and family income as examples.

Answer

A mediator lies on the path from cause to outcome: fiber could change gut microbes, which could make chemicals that affect mood, so microbes would be a mediator. A confounder sits outside the path and affects both ends: family income can affect how much fiber people eat and also their stress and mood, creating a link even if fiber did nothing.

1. Explain how evidence for a link between ultra-processed food and anxiety could be rated "convincing" in class but "low" in quality.

Answer

"Convincing" means the association comes from large numbers of people, is consistent across studies, and is very unlikely to be a statistical fluke (it doesn't mean the effect is big). "Low quality" means the studies are mostly observational snapshots, so they can't rule out confounding or reverse causation. The link is solid; what causes it isn't.

Apply

1. Using the Diet Pattern Explorer, set the true effect to none and record the correlation with each hidden factor switched on by itself. Which factor creates the strongest fake link, and why might that be?
2. A news story says, "People who take daily vitamins have better mood, study finds." Identify how healthy user bias could explain this finding, and name two other habits that might differ between vitamin users and non-users.

Analyze

1. Compare SMILES, HELFIMED, and PREDIMED using four of the six claim questions. Why do you think PREDIMED, the largest, found no significant overall effect on new depression?
2. Food insecurity affected 13.7% of US households in 2024. Analyze two separate ways food insecurity could distort an observational study of diet and mood.

Evaluate

1. A school wellness newsletter wants to print: "Science shows the Mediterranean diet cures depression." Evaluate this sentence and rewrite it so it earns an accurate Hype Meter grade.
2. Some people argue that because diet trials can't be blinded, they should never be trusted. Evaluate this argument. What design features could make a diet trial more trustworthy even without blinding?

Create

1. Design a randomized trial to test whether adding fermented foods improves mood in high school students. Describe your groups, how you'd randomize, what you'd measure and when, how you'd protect students with eating disorder risk or gut conditions, and what result would support your hypothesis.
2. Create a short, food-positive message (under 100 words) for a school cafeteria poster about food and mood that is accurate, avoids good/bad food language, doesn't mention body size, and would earn a fair Hype Meter grade.

Key Takeaways

- Nutrition researchers study whole dietary patterns, such as Mediterranean-style eating or diets high in ultra-processed food, rather than single foods.
- Possible gut-brain links include fiber feeding microbes, fermented foods raising microbe diversity, and polyphenols being processed by microbes, but most mood evidence for these is indirect or from animals.
- Observational studies link ultra-processed food with depression and anxiety symptoms (a Moderate association), but confounding, healthy user bias, and reverse causation mean cause is not proven.
- Randomized controlled trials balance hidden factors by chance. A few small trials, including SMILES (remission 32.3% vs 8.0%), suggest diet support may help adults with depression as an add-on to care (Preliminary).
- Dose-response patterns make cause more believable but aren't proof; mediators explain how an effect happens, while confounders create fake links.
- Healthy eating isn't equally easy for everyone: in 2024, 13.7% of US households were food insecure.
- Food is nourishment, culture, and comfort, not a moral test. Restrictive diets aimed at mood can raise eating disorder risk, and diet never replaces treatment for depression.

You can read a food study like a scientist!



You can now spot confounders, reverse causation, and healthy user bias, and you know why a coin flip is so powerful. Next, in Chapter 16, we'll use those same tools on one of the biggest gut-health markets of all: probiotics, prebiotics, and so-called "psychobiotics."

Quiz: Food and Mood

Test your understanding of Chapter 15. Choose the best answer, then click **Show Answer** to check.

Question 1

What is a dietary pattern?

A. A single nutrient that researchers measure in the blood

B. The overall combination of foods and drinks a person usually eats over time, studied as a whole

C. A strict meal plan that a doctor prescribes

D. The order in which foods are eaten during one meal

Show Answer

The correct answer is **B**. Researchers study whole patterns because foods come in bundles, and people who eat more of one food often eat differently in other ways too. Option A describes studying one nutrient at a time, which is exactly what pattern research tries to move beyond.

Concept Tested: Dietary Pattern **Bloom's Level:** Remember

Question 2

What made the SMILES trial a randomized controlled trial?

A. Participants chose whether they wanted diet support or social support.

B. It included more than 10,000 people.

C. Chance decided whether each participant got dietitian support or social support.

D. Nobody, including the participants, knew which group they were in.

Show Answer

The correct answer is **C**. Random assignment is what makes a trial randomized, and it balances hidden factors between groups on average. Option D is wrong: participants knew their group; only the people rating depression were blinded. Option B is wrong too, since SMILES enrolled just 67 people.

Concept Tested: SMILES Trial **Bloom's Level:** Remember

Question 3

About how much fiber does the average person in the US eat each day, according to the national survey data in this chapter?

A. About 16 grams

B. About 31 grams

C. About 50 grams

D. About 5 grams

Show Answer

The correct answer is **A**. Average intake was 16.2 grams a day in the 2009 to 2010 national survey, while the 2020 to 2025 Dietary Guidelines suggested about 25 grams for girls and 31 grams for boys aged 14 to 18. Option B is the suggested amount for teen boys, not what people actually eat; that difference is the dietary fiber gap.

Concept Tested: Dietary Fiber Gap **Bloom's Level:** Remember

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Question 4

Why can people who take daily vitamins look healthier in observational studies, even if the vitamins themselves do little?

A. Because vitamins always improve mood within a week

B. Because people who choose one health behavior often have other healthy habits and advantages

C. Because observational studies randomly assign who takes vitamins

D. Because vitamins are ultra-processed foods

Show Answer

The correct answer is **B**. This is healthy user bias: people who follow one piece of health advice often also sleep more, exercise more, and see doctors regularly, which makes the behavior look more helpful than it is. Option C is wrong because observational studies don't assign anything; that's what makes them vulnerable to this bias.

Concept Tested: Healthy User Bias **Bloom's Level:** Understand

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Question 5

A 2024 umbrella review rated the link between ultra-processed food and anxiety as "convincing" evidence of an association, but "low" quality. What does that combination mean?

A. The link is probably a statistical fluke.

B. Ultra-processed food has been proven to cause anxiety.

C. The studies were randomized trials with many dropouts.

D. The link is consistent and unlikely to be chance, but the mostly observational designs can't show what causes it.

Show Answer

The correct answer is **D**. "Convincing" describes how statistically solid and consistent the association is (not how big the effect is); "low quality" reflects that the studies were mostly observational snapshots that can't rule out confounding or reverse causation. Option B is the common misreading that turns a strong link into a proven cause.

Concept Tested: Ultra-Processed Food **Bloom's Level:** Understand

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Question 6

Researchers suggest fiber might improve mood because gut microbes turn fiber into short-chain fatty acids that could affect the brain. In this pathway, what role do the gut microbes play?

A. A mediator variable, because they lie on the path between fiber and mood

B. A confounder, because they affect both fiber intake and mood from outside the path

C. A placebo, because they have no effect

D. A control group

Show Answer

The correct answer is **A**. A mediator carries the effect along the causal path and explains how a cause works. Option B describes a confounder, which sits outside the path and affects both ends (like family income), creating a link without being part of the mechanism.

Concept Tested: Mediator Variable **Bloom's Level:** Understand

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Question 7

A student uses the Diet Pattern Explorer with the true effect set to none and all hidden factors on. In observational mode she sees a correlation of about -0.6. What should she conclude?

A. Diet strongly improves mood in this simulated world.

B. The simulation is broken, because there should be no correlation at all.

C. The hidden factors created the link, so the correlation does not show that diet affects mood.

D. Randomized trials would show the same -0.6 link.

Show Answer

The correct answer is **C**. She set the true effect to zero, so the entire link comes from food access, sleep, and low mood changing eating. Option D is wrong because a coin flip balances those hidden factors, so the trial shows only a small chance difference.

Concept Tested: Observational Study **Bloom's Level:** Apply

Question 8

Maya, a fictional 16-year-old, reads that a Mediterranean diet helps depression and decides to cut out every food not on a list she found online, even though she feels anxious about eating. Based on the chapter, what is the biggest concern?

A. She won't get enough olive oil.

B. Strict, self-imposed food rules can raise eating disorder risk, and the trials added diet support rather than cutting food groups.

C. Mediterranean diets are proven to make depression worse.

D. Online lists are always more accurate than dietitians.

Show Answer

The correct answer is **B**. Restrictive eating and anxiety about food can be warning signs for an eating disorder, and none of the trials in this chapter tested cutting out food groups for mood. Maya would do better talking with a doctor or registered dietitian. Option C is wrong because the small trials found possible benefits, not harm, when diet support was added to care.

Concept Tested: Eating Disorder Risk **Bloom's Level:** Apply

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Question 9

The SMILES trial found remission in 32.3% of the diet group versus 8.0% of the social support group, while the much larger PREDIMED trial found no significant overall effect of a Mediterranean diet on new depression. Which analysis best explains how both can be true?

A. PREDIMED must have measured depression the wrong way.

B. SMILES proves diet cures depression, so PREDIMED can be ignored.

C. Both trials studied the same people in the same way, so they should agree exactly.

D. They asked different questions in different people: SMILES treated adults already depressed for 12 weeks, while PREDIMED tried to prevent new depression in older adults at high heart risk.

Show Answer

The correct answer is **D**. SMILES tested treatment as an add-on in 67 adults with depression; PREDIMED tested prevention in 3,923 adults aged 55 to 80. Different questions, groups, and outcomes can give different answers, and SMILES was also small and not fully blinded. Option B overstates a single small trial.

Concept Tested: Mediterranean Diet **Bloom's Level:** Analyze

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Question 10

An observational study finds that teens from families with less money eat fewer fresh vegetables and report more low mood. Which analysis best explains why this doesn't show that vegetables improve mood?

A. Food insecurity and money stress could affect both diet and mood, acting as confounders.

B. Vegetables are never linked to mood in any study.

C. Teens can't report their mood accurately.

D. The study should have used mice instead.

Show Answer

The correct answer is **A**. Families with limited money may have less access to fresh food and also more financial stress, which affects mood, so the link could appear even if vegetables did nothing. In 2024, 13.7% of US households were food insecure at some point. Option D is wrong because a mouse study couldn't capture income or human mood in the same way.

Concept Tested: Food Insecurity **Bloom's Level:** Analyze

Chapter 16: Probiotics, Prebiotics, and "Psychobiotics"

Summary

Probiotic capsules, prebiotic sodas, and "mood" supplements fill store shelves and social media feeds. This chapter defines the products scientists actually mean (probiotics, prebiotics, synbiotics, and postbiotics), explains why the exact strain on the label matters, and shows how lightly supplements are regulated in the United States compared with medicines. It covers who should be careful with probiotics, including premature babies and people with weak immune systems. Then it follows the "psychobiotic" idea from a famous mouse study to a human trial that did not work, and teaches the tools you need to read probiotic trials yourself: systematic reviews, effect sizes, primary outcomes, publication bias, and replication.

Concepts Covered

1. Probiotic
2. Prebiotic
3. Synbiotic
4. Postbiotic
5. Psychobiotic
6. Lactobacillus
7. Bifidobacterium
8. Strain Specificity
9. Colony-Forming Unit
10. Dietary Supplement Regulation
11. Probiotic Safety
12. Systematic Review
13. Effect Size
14. Primary Outcome
15. Publication Bias
16. Replication Failure

Prerequisites

- Chapter 3: Meet the Microbiome (microbiome, dysbiosis, germ-free mice)
- Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier (how microbes ferment fiber)
- Chapter 11: Anxiety, Depression, and the Gut (meta-analysis, symptom questionnaires)
- Chapter 13: Autism, ADHD, and the Gut (open-label vs placebo-controlled trials, sample size)
- Chapter 15: Food and Mood (randomized controlled trials)

A capsule with a big promise



Probiotics are probably the gut-brain product you'll see advertised most, and many of the ads talk about mood, stress, or focus. This chapter gives you the vocabulary and the trial-reading skills to look past the label and ask what was actually tested, in whom, and what happened. Those same skills work on almost any supplement claim you'll ever meet.

16.1 "Calm in a Capsule"

Sam's older cousin Dev posts a lot about supplements. This week it's a bottle with a sunrise on the label and the words "Calm in a Capsule: the psychobiotic for stress, mood, and focus. 50 billion CFU!" Dev tags Sam in the comments: "Bro, this would fix your race nerves AND your stomach." (Sam and Dev are fictional.)

Sam has IBS with mixed bowel habits, and his symptoms flare before big tests and races. He's been learning gut-directed relaxation, and it helps. He's also learned to be suspicious of anything that promises to fix two problems at once. At lunch he shows the post to his best friend Riya, who has Crohn's disease. Riya shrugs. "I asked Dr. Alvarez about probiotics once. She said it depends on which one and what for, and that for Crohn's they're mostly still being studied." Sam looks at the bottle again. Which one? For what? The label says "psychobiotic," but what does that even mean, and who checked that this capsule does anything?

Those are the right questions. By the end of this chapter, you'll be able to read Dev's bottle the way a scientist would.

16.2 Seeds, Fertilizer, and the Garden in Your Gut

Picture your gut microbiome (the trillions of microbes living in your intestines, from Chapter 3) as a garden. There are two obvious ways to change a garden. You can plant new seeds, or you can add fertilizer that helps certain plants already growing there. You can also do both at once. Or, stranger, you could spread something made from plants that are no longer alive, like mulch, and still change how the garden grows.

Scientists have names for each of these approaches. The definitions below come from consensus statements written by panels of the International Scientific Association for Probiotics and Prebiotics (ISAPP), a scientific group that meets to agree on how these words should be used.

A **probiotic** is defined as "live microorganisms that, when given in adequate amounts, confer a health benefit on the host" (ISAPP, 2014, keeping the wording used by the United Nations Food and Agriculture Organization and the World Health Organization). Three parts of that definition matter. The microbes must be **alive** when you take them. They must be given in a **big enough amount**. And they must have a **demonstrated health benefit**. A yogurt full of live bacteria is not automatically a probiotic in this scientific sense unless a benefit has been shown.

A **prebiotic** is "a substrate that is selectively utilized by host microorganisms conferring a health benefit" (ISAPP, 2017). In plain words, it is food for your microbes, but a picky kind of food: it feeds certain microbes more than others, and it has to produce a health benefit. Many prebiotics are types of fiber, which connects to the fermentation story in Chapter 6. The 2017 statement says prebiotics are not limited to carbohydrates, and that a health benefit has to be shown before something earns the name.

A **synbiotic** is "a mixture of live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host" (ISAPP, 2020). The ISAPP panel described two kinds. A *complementary* synbiotic is simply a probiotic plus a prebiotic in the same product. A *synergistic* synbiotic is designed so the food part is chosen to feed the live microbes it comes with.

A **postbiotic** is "a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" (ISAPP, 2021). "Inanimate" means no longer alive. Under this definition, a postbiotic must contain inactivated microbial cells or cell parts. A purified chemical made by microbes, all by itself, doesn't count.

Term	Garden comparison	What it is	Must show a health benefit?
Probiotic	Planting seeds	Live microbes in adequate amounts	Yes
Prebiotic	Fertilizer for certain plants	A substance gut microbes use selectively	Yes
Synbiotic	Seeds plus fertilizer	Live microbes plus a substance microbes use	Yes
Postbiotic	Mulch made from old plants	Inactivated microbes or their parts	Yes

Notice the last column. Every one of these scientific definitions requires a **health benefit**. That's the part marketing tends to skip. A product can contain live bacteria or fiber and still not meet the scientific definition, because nobody has shown it does anything for people.

The benefit is part of the definition



When I read "probiotic" on a label, I remind myself that scientists only use the word for live microbes with a proven benefit. So the real question is never "Does it contain bacteria?" but "Which benefit was shown, for which strain, in which people?"

16.3 The Usual Suspects: Lactobacillus and Bifidobacterium

If you turn a few probiotic bottles around, you'll see the same two names again and again. The National Center for Complementary and Integrative Health (NCCIH), part of the US National Institutes of Health, says the most common probiotic bacteria belong to these two groups. Yeasts such as *Saccharomyces boulardii* are also used.

Lactobacillus is a group of bacteria known for turning sugars into lactic acid. Lactic acid bacteria are used to make yogurt and other fermented foods, and some live naturally in the human body. There's a twist for anyone reading older labels and studies. In 2020, a team of microbiologists led by Zheng compared the full genomes of these bacteria and found that the old genus *Lactobacillus*, which then held 261 species, was really many different groups. They split it into 25 genera. Some famous probiotic species got new first names: *Lactobacillus rhamnosus*, for example, is now *Lacticaseibacillus rhamnosus* (see the official List of Prokaryotic names with Standing in Nomenclature entry, which credits the 2020 Zheng paper). The informal word "lactobacilli" is still used for the whole family of former members. So if a 2011 paper and a 2025 bottle use different names, they may mean the same microbe.

Bifidobacterium is another large group of bacteria that live naturally in the human gut. Like lactobacilli, they ferment sugars and some fibers, which is one reason they show up so often in probiotic and synbiotic products.

Every strain is an individual

Here's the most important idea in this section. A species is not specific enough. Think about how people are named. "Smith" tells you a family, "Jordan Smith" narrows it down, but you need an address to find the one Jordan Smith you mean. Bacteria are named the same way: a **genus** (family name, like *Lacticaseibacillus*), a **species** (like *rhamnosus*), and a **strain** code (like GG or JB-1) that pins down one specific lineage grown in a lab.

Strain specificity is the finding that a probiotic's effects belong to a particular strain, used for a particular condition, so a result from one strain cannot be assumed to apply to another strain, even one from the same species. NCCIH puts it simply: if one kind of *Lactobacillus* helps prevent an illness, that doesn't mean another kind of *Lactobacillus*, or any *Bifidobacterium*, would do the same thing.

The best evidence for strain specificity comes from a 2018 systematic review by McFarland, Evans, and Goldstein, which looked at 228 trials of probiotics with identifiable strains. They found that effects depended

on both the strain and the disease. For example, among *Lactobacillus* products tested for preventing diarrhea caused by antibiotics in adults, some specific strains and mixtures worked while other *Lactobacillus* strains did not. They also found that a single strain could help with one condition but not another. Their warning for scientists: reviews that lump different probiotics together can reach misleading conclusions.

Strain specificity matters for Dev's bottle. A label that says only "*Lactobacillus* blend" or "bifidobacteria" doesn't tell you which strains you're getting, so it's impossible to match the product to any study.

Hype Meter: "All probiotics are basically the same, so just grab any one"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. A 2018 systematic review of 228 trials found that probiotic effects depend on both the specific strain and the specific condition, and NCCIH says a benefit from one strain doesn't carry over to others. Strains from the same species can behave differently, and a strain that helps one problem may not help another. **What would change the grade:** Large head-to-head trials showing that many different strains give the same benefit for the same condition. So far, the evidence points the other way.

16.4 Reading the Label: What "50 Billion CFU" Means

Dev's bottle brags about "50 billion CFU." That sounds impressive. What is it actually counting?

A **colony-forming unit** (CFU) is a count of how many microbes in a sample are alive and able to multiply. To measure it, scientists spread a diluted sample on a dish of nutrient gel and wait. Each living cell (or tiny clump of cells) that can grow forms a visible dot called a colony. Count the colonies, multiply by how much the sample was diluted, and you get CFU. Dead bacteria don't form colonies, so they don't count. That's why probiotic doses are given in CFU: the definition of a probiotic requires live microbes.

Three things about CFU trip people up.

1. **Bacteria die on the shelf.** An ISAPP guide to probiotic labels, written by microbiologist Mary Ellen Sanders (updated in 2025), explains that most strains lose live cells during storage, some faster than others. A count printed "at time of manufacture" may be much higher than what's alive when you open the bottle months later. Guidance from FAO/WHO calls for listing the minimum live count at the **end of shelf life**.
2. **A big total can hide a small dose of the strain that matters.** In a product with many strains, one total CFU number doesn't tell you how much of each strain is inside. The bulk could be a cheaper strain rather than the one with evidence behind it.
3. **More is not automatically better.** The amount that matters is the amount shown to work in a study of that strain. A product with ten times more CFU of an untested strain isn't ten times better; it's untested at a higher number.

The same ISAPP guide describes a survey of supplements sold in Washington, DC: 45% didn't list strain designations, and only 35% could be linked to evidence of a health benefit for that strain at that dose.

What a careful label shows	What a weak label shows
Genus, species, and strain code for each microbe	Only "probiotic blend" or a genus name
CFU guaranteed at the end of shelf life	CFU "at time of manufacture" only
A dose matching a published study	A huge number with no study
Storage instructions	None

Match the strain, the dose, and the condition



A probiotic claim is only as good as three matches: the same strain that was studied, at about the same dose, for the same health problem. If any of the three is missing, the study doesn't really apply to the bottle in your hand.

16.5 Who Checks the Bottle? Dietary Supplement Regulation

Most people assume that anything sold in a pharmacy has been tested and approved by the government. For medicines, that's true. For supplements, it isn't.

Dietary supplement regulation is the set of US rules for products like vitamins, herbs, and most probiotics, which, unlike medicines, do not need FDA approval for safety or effectiveness before they are sold. In 1994, Congress passed the Dietary Supplement Health and Education Act (DSHEA), which defined "dietary supplement" and set out the FDA's role. According to the FDA, under DSHEA:

- The FDA does **not** have the authority to approve dietary supplements before they are marketed.
- The companies that make and sell supplements are **responsible for** making sure their products are safe and correctly labeled before they go on sale.
- The FDA can take action against an unsafe or mislabeled product **after** it reaches the market.

NCCIH explains that the FDA might treat a probiotic product as a dietary supplement, a food ingredient, or a drug, depending on how it's meant to be used. Many probiotics are sold as supplements. If a company wants to market a probiotic as a drug to treat a disease, it must prove the product is safe and effective in clinical trials and get FDA approval first. That's the path the medicines in Chapter 17 had to travel.

What can a supplement label say? NCCIH notes that supplement labels may make claims about how a product affects the structure or function of the body (such as "supports digestive health") without FDA approval. They aren't allowed to claim the product treats, cures, or prevents a disease. That's why many bottles carry a small legally required disclaimer, which the FDA quotes: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." (Chapter 20 looks more closely at these "structure-function" claims and how advertising is policed.)

Put these facts together and Dev's bottle looks different. "Calm in a Capsule" is almost certainly a dietary supplement. No government agency checked that it reduces stress before it went on sale, and words like "psychobiotic" are marketing language, not an FDA category.

	New prescription drug	**Dietary supplement (most probiotics)**
FDA approval before sale?	Yes	No
Must prove it works first?	Yes, in clinical trials	No
Who is responsible for safety before sale?	Company, reviewed by FDA	Company
Can it claim to treat a disease?	Yes, for its approved use	No

16.6 "Natural" Doesn't Mean Risk-Free: Probiotic Safety

Probiotics are often described as completely harmless. For most healthy people, that's close to true, but "close" matters.

Probiotic safety refers to the risks of taking live microbes, which are low for most healthy people but higher for people who are very sick, have weakened immune systems, or were born very early, because the microbes can occasionally cause infections. NCCIH says probiotics have a long history of apparently safe use, especially in healthy people. But it also says few studies have looked at safety in detail, so there isn't solid information on how often side effects happen or how serious they are. The risk of harm is greater in people with severe illnesses or weakened immune systems, and NCCIH says doctors should weigh the risks carefully for high-risk people such as premature infants and seriously ill hospital patients.

Why would a "good" bacterium cause harm? A healthy gut lining and immune system keep microbes inside the gut, where they belong. In a very premature baby, whose gut and immune system are still developing, or in a person whose immune system is weakened by illness or treatment, live microbes from a capsule can occasionally cross into the bloodstream and cause an infection. Products can also be contaminated with organisms that aren't supposed to be there. In a 2015 report, the Centers for Disease Control and Prevention

described a baby born at 29 weeks who died of a rare fungal infection after receiving a probiotic powder; unopened bottles from the same batch grew the same fungus.

The clearest warning came in 2023. On October 26, 2023, the FDA announced that probiotic products used in hospitals for preterm infants, often to try to prevent a serious gut disease called necrotizing enterocolitis, had contributed to invasive disease, including **one infant death in 2023**, and had been associated with **more than two dozen other reported harmful events in the United States since 2018**. The FDA sent warning letters to two companies for illegally selling probiotics to treat or prevent disease in preterm infants, and it stated that it "has not approved any probiotic product for use as a drug or biological product in infants of any age."

There's a real scientific debate behind this. In 2020, the American Gastroenterological Association (AGA) guideline on probiotics conditionally suggested certain strains for preventing necrotizing enterocolitis in preterm, low-birth-weight babies. Three years later, the FDA warned about serious infections and said no probiotic is approved as a drug for infants. Both statements are real, and they point in different directions. That's why decisions about very sick babies belong to the hospital care team and the family together, not to a supplement label.

Hype Meter: "Probiotics are always safe because they're natural"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. Probiotics have a long record of apparently safe use in healthy people, but NCCIH says risk is greater for people with severe illness or weakened immune systems, and few studies have measured side effects in detail. In 2023, the FDA reported that probiotics given to hospitalized preterm infants contributed to invasive disease, including a death. "Natural" describes where something comes from, not how safe it is for a particular person. **What would change the grade:** Nothing about the "always" part. Better safety studies could show more precisely who is at risk and who isn't.

What does the AGA 2020 guideline say about the gut conditions in this book? It recommends using probiotics for IBS, Crohn's disease, and ulcerative colitis only in clinical trials, not as routine treatment. It suggests specific strains for a few uses, such as preventing *C. difficile* infection in people taking antibiotics and a specific eight-strain mix for pouchitis (inflammation of a surgically made pouch after colon removal), and it suggests against probiotics for children with acute infectious diarrhea. That matches what Dr. Alvarez told Riya: for Crohn's, probiotics are still a research question.

For families

It's natural to want to do something when your child or sibling is sick, and a probiotic can feel like a safe, hopeful step. Before giving one, bring the actual bottle to the care team, especially if your child is on medicines that affect the immune system, is going through cancer treatment, or was born very early. Asking "Is there any reason this could be risky for my child?" is not an insult to the doctor; it's exactly the question they want you to ask. And if a teen in your family is skeptical of a product a relative keeps pushing, that skepticism is a sign of good thinking, not stubbornness.

16.7 Psychobiotics: From a Mouse Maze to a Human Trial

Now to the word on Dev's label. In 2013, three researchers in Cork, Ireland (at University College Cork and the nearby Teagasc Moorepark research centre), Timothy Dinan, Catherine Stanton, and John Cryan, published a paper titled "Psychobiotics: a novel class of psychotropic." A **psychobiotic**, in their original definition, is a live organism that, when taken in adequate amounts, produces a health benefit in patients with psychiatric illness. Later papers stretched the term to include other ways of changing the microbiome to help mental health, but the 2013 definition is the original. The same paper said that results from large placebo-controlled studies were still "awaited."

Two things follow. "Psychobiotic" is a **research term**, not an approved product category; no agency checks whether a product labeled "psychobiotic" helps anyone. And by the original definition, it would apply only to organisms shown to benefit people with psychiatric illness, which is a high bar.

The mouse study that launched a thousand headlines

Much of the excitement traces back to a 2011 study in the journal *PNAS* by Javier Bravo and colleagues, also in Cork. They fed mice a specific strain, *Lactobacillus rhamnosus* JB-1, for several weeks. Compared with control mice, the treated mice showed less anxiety-like and depression-like behavior in standard lab tests, and lower levels of corticosterone (the mouse version of the stress hormone cortisol) after stress. The researchers also found changes in brain receptors for GABA, the brain's main "calming" chemical messenger, in several brain regions.

The most striking part was an experiment that tested cause. In mice whose vagus nerve had been cut (a vagotomy), the bacteria had **no effect** on behavior or brain receptors. That suggested the bacteria's signal traveled from the gut to the brain along the vagus nerve, the gut-brain nerve highway from Chapter 2. It's a clever experiment, and it fit the gut-brain story perfectly.

Notice the type of evidence: **mice**, and an **experiment that tested cause**, but only in mice.

The human trial that didn't work

Six years later, much of the same research group took the natural next step and gave the same strain to people. In a 2017 study in *Brain, Behavior, and Immunity*, Kelly and colleagues gave *L. rhamnosus* JB-1 or a placebo to 29 healthy men in an 8-week randomized, placebo-controlled crossover design (each man took the probiotic for 4 weeks and the placebo for 4 weeks, in random order, without knowing which was which). They measured mood, anxiety, stress, sleep quality, the stress hormone response to a lab stress test, inflammation, memory and attention, and brain waves on EEG.

The probiotic did no better than placebo on any of these. The paper's title asked, "Lost in translation?" The authors noted that the original mouse work used an especially anxious strain of mouse, while the human volunteers were healthy, and they called for studies in people with stress-related disorders.

This pair of studies is a textbook example of **replication failure**: when a later study tests the same idea and does not find the original result. A replication failure doesn't automatically mean the first study was wrong. Here, the second study changed several things at once (mice to humans, anxious animals to healthy people, and a small group of 29 men), so it can't say whether JB-1 would help people with anxiety. What it does show is that a strong mouse result didn't carry over to healthy men. That's common. As Chapter 20 explains, only about one in three highly cited animal studies were later tested successfully in human trials.

Don't let a mouse speak for you



I love the JB-1 mouse experiment, and it really does show that a gut microbe can change mouse behavior through the vagus nerve. But when the same strain was tested in healthy men, nothing happened. When an ad leans on a mouse study, the honest summary is "promising in mice, unproven in people."

16.8 What Do All the Trials Say? Reading the Evidence

One study can't settle a question, especially a small one. So how do scientists combine many trials? And why do different reviews of the same topic sometimes disagree?

Systematic reviews and meta-analyses

A **systematic review** is a study of studies that uses a written plan to search for every relevant study on a question, judge each one's quality, and summarize the results, so that the conclusion doesn't depend on which studies an author happened to pick. Think of the difference between asking three friends what they thought of a movie and reading every review in a big database using fixed rules. The "systematic" part is what makes it trustworthy: the search terms, the rules for including studies, and the quality checks are all written down in advance, often registered publicly.

Many systematic reviews then combine the numbers from the included trials into one overall estimate. That step is a meta-analysis, which you met in Chapter 11. Not every systematic review includes a meta-analysis

(sometimes the studies are too different to combine), but most of the probiotic reviews in this chapter do both.

How big is the effect?

To compare trials that used different questionnaires, scientists convert results into an **effect size**: a number that describes how big a difference is between groups, often measured in standard deviations (a unit for how spread out people's scores are), so that results from different scales can be compared. A common version is called *d* or the standardized mean difference. An effect size of 0 means no difference. Bigger numbers mean bigger differences, whatever the sign. (In depression studies, a negative number usually means the treatment group's scores dropped more, which is good.)

Effect size answers a different question from "Was there an effect?" A huge study can detect a real but tiny effect that hardly matters to anyone, and a small study can produce a big-looking effect by luck. Researchers often describe an effect around 0.2 standard deviations as small. In a 2019 review, Liu and colleagues called an effect of 0.24 "small" and one of 0.73 "medium-to-large."

Different reviews, different answers

Here's what four recent reviews of probiotics for depression found. (Liu also pooled prebiotic trials, and Pan pooled a wider group of "microbiome-targeted" treatments that includes probiotics.) All are human studies, and all pool randomized controlled trials that compare a treatment group with a control group, so they are designed to test cause. But look how much they differ.

Review	Trials included	Main finding for probiotics and depression	Notes
Liu et al., 2019	34 controlled trials (probiotics and prebiotics)	Small effect, d = 0.24	Prebiotics showed no effect; bigger effect in clinical samples, and 0.73 in a preliminary analysis of people with a psychiatric diagnosis
Rahmannia et al., 2024	12 trials, 707 people	Improvement on one questionnaire (BDI), not on three others	Authors urge cautious interpretation
Asad et al., 2025	23 trials, 1,401 patients with a diagnosis (18 trials tested probiotics for depression)	Large effect, about 0.96, but results varied a lot	High heterogeneity (trials disagreed with each other)

Review	Trials included	Main finding for probiotics and depression	Notes
Pan et al., 2025	34 trials of "microbiome-targeted" treatments, including probiotics	Small effect, about 0.26	Benefit in Asian studies, not European ones; no benefit beyond 12 weeks

Why don't they agree? They included different trials, different people (healthy volunteers versus people with a diagnosis), different strains, and different lengths of treatment. Strain specificity alone means "probiotics" in one review might be completely different products from "probiotics" in another. When a review reports **high heterogeneity**, that's a warning that the trials inside it disagree so much that one average number may be misleading.

The trap of many outcomes

The Rahmannia 2024 review deserves a closer look because it's often summarized as "probiotics reduce depression (12 trials, 707 people)." Here's what the abstract actually reports for its four depression scales:

Depression scale	Who fills it out	Result
Beck Depression Inventory (BDI), 7 trials	The patient	Scores dropped more with probiotics (about 2.7 points)
Hamilton Depression Rating Scale (HAMD)	A clinician	No significant difference
Depression Anxiety Stress Scales (DASS)	The patient	No significant difference
Montgomery-Åsberg Depression Rating Scale (MADRS)	A clinician	No significant difference

One out of four scales showed a benefit. Is that a real effect that only the BDI picked up, or a chance result? The review can't tell, and its authors say the mixed results call for caution.

This is why good trials name a **primary outcome**: the one main measurement a study commits to in advance as the test of whether the treatment works, written down before the results are known. Other measurements are called secondary outcomes. Picking the primary outcome first matters because of a simple fact about chance. If a treatment does nothing, any single measurement still has a small chance of looking "significant" just by luck. Measure one thing and you'll rarely be fooled. Measure ten things and report whichever looked

best, and you'll be fooled often. A trial that names its primary outcome ahead of time can't quietly switch to whichever result looked best.

The missing studies: publication bias

There's one more trap, and it's sneaky because you can't see it in any single paper. **Publication bias** is the tendency for studies with exciting, positive results to be published more often (and faster) than studies that found nothing, so the published research makes a treatment look better than it really is.

The most famous demonstration comes from antidepressant medicines, not probiotics. In 2008, Turner and colleagues compared 74 antidepressant trials that companies had registered with the FDA against what was published in medical journals. Almost all the positive trials were published, but most of the negative or questionable ones were either never published (22 trials) or were published in a way that made the result sound positive (11 trials). Reading only the journals, 94% of trials looked positive. The FDA's full records showed about 51% were. Because the negative studies were missing, the published research made the drugs' effect look about 32% bigger overall than the full set of data did.

If publication bias can distort the evidence for heavily regulated medicines, it can affect probiotic research too, where many trials are small. Systematic reviews try to detect it with statistical checks, and trial registries (public lists where trials are recorded before they start) help reveal studies that disappeared. But a meta-analysis of the published trials can only be as honest as the trials that got published.

Hype Meter: "Probiotics treat depression and anxiety"

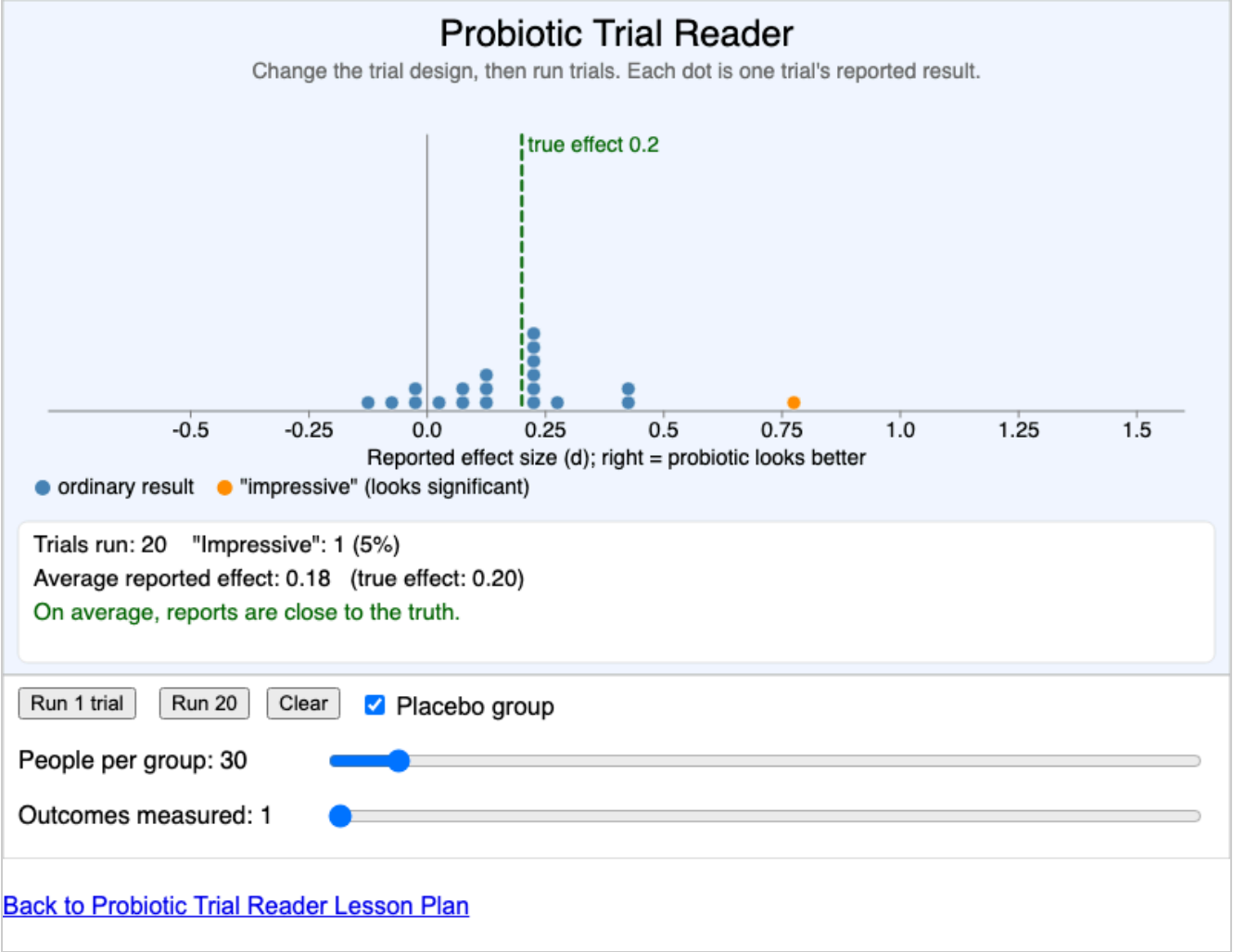
Strong	Moderate	**Preliminary**	Hype

Verdict: Preliminary. Several meta-analyses of human randomized trials report some benefit, but the estimates range from small to large, the trials disagree a lot, and the results depend on the strain, the people, and the questionnaire. A 2024 review of 12 trials (707 people) found improvement on one depression scale but not on three others, and one of the best-designed add-on trials so far (Section 16.10) was a small pilot. No probiotic is approved to treat depression or anxiety. **What would change the grade:** Large, preregistered, placebo-controlled trials of a specific strain in people with a diagnosed condition, with one primary outcome, that are then repeated by independent teams.

16.9 Try It Yourself: The Probiotic Trial Reader

Why do small trials sometimes produce exciting results for treatments that do very little? You can see it happen. In the simulation below, a made-up probiotic has a small true effect, about 0.2 standard deviations, similar in size to the small pooled effects some reviews report. Every time you press a button, the sim runs pretend trials and plots the result each trial would report. You choose how many people are in each group, how many outcomes each trial measures (with the "best" one reported, like an ad would), and whether the trial has a placebo group.

Diagram: Probiotic Trial Reader



Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch16-trial-reader/main.html

Open the Probiotic Trial Reader fullscreen

MicroSim specification: Probiotic Trial Reader

Type: microsim **sim-id:** ch16-trial-reader
Library: p5.js
Status: Implemented
Bloom Level: Evaluate
Bloom Verb: judge
Learning Objective: The learner will judge how trial size, number of outcomes measured, and the presence of a placebo group change how much confidence a reported probiotic result deserves.

Canvas: 440 px drawing area plus 120 px controls (iframe 562 px); responsive to about 380 px wide.

Controls: Run 1 trial, Run 20 (trials), Clear; Placebo group checkbox (default on); People per group slider (10 to 300, default 30); Outcomes measured slider (1 to 10, default 1).

Rules: True effect d = 0.2 (illustrative). For each trial and each outcome, the measured effect = true effect + random noise with standard error $\sqrt{2/n}$. The trial reports its best (largest) outcome. Without a placebo group, a placebo response of 0.4 is added (everyone improves) and noise uses $\sqrt{1/n}$. A result is flagged "impressive" if it is more than about 1.96 standard errors above zero. Results are drawn as a dot plot on an effect-size axis with lines at 0 and at the true effect.

Feedback: A panel shows trials run, the share flagged impressive, the average reported effect, and how that compares with the true effect.

Provenance: Section 16.8 (primary outcome, effect size, publication bias). All numbers are illustrative, not from a real trial.

Start with the defaults (30 people per group, 1 outcome, placebo group on) and press **Run 20** a few times. The dots scatter widely around the true effect line, and some land far to the right. Those are the trials that would make headlines, even though the true effect never changed. Now press **Clear** (do this every time you change a setting, so old dots don't mix in), slide **People per group** to 300, and run again. The dots crowd close to the true effect, and the average reported effect lands near 0.2.

Next, set people per group back to 30 and raise **Outcomes measured** to 10. Each trial now reports its best of ten outcomes, and the average reported effect jumps well above the truth, with many more "impressive" results. Finally, uncheck **Placebo group**. With no comparison group, the placebo response gets counted as if it were the probiotic's effect. Ask yourself which combination of settings looks most like a typical supplement ad, and which looks like a trial you'd trust.

What this model leaves out

- The true effect is fixed at a made-up 0.2. In reality, nobody knows the true effect, and it probably differs by strain, condition, and person.
- Real outcomes in one trial are related to each other (people who feel better on one scale often feel better on another), so the "best of many outcomes" boost is usually smaller than in the sim.
- Trial length isn't modeled. Real effects might grow, fade, or disappear over time (one 2025 review found no benefit beyond 12 weeks).
- The sim leaves out dropouts, people guessing their group, funding, and publication bias, all of which can shift real results.
- The "impressive" flag is a simplified version of statistical significance, which Chapter 20 explains properly.

16.10 How to Read a Gut-Brain Claim: A Probiotic Add-On Pilot Trial

Let's apply the six questions to one of the best-designed recent probiotic trials in people with depression. In 2023, Nikolova and colleagues at King's College London published a trial in *JAMA Psychiatry*. They enrolled adults aged 18 to 55 with major depressive disorder who were already taking an antidepressant but hadn't fully improved. For 8 weeks, half took a multistrain probiotic (8 billion CFU a day, a 14-strain commercial product called Bio-Kult Advanced) and half took a placebo, added to their usual medicine. Neither the participants nor the researchers knew who got which (double-blind). Of 49 people analyzed, 24 got the probiotic and 25 got placebo. Only 8% dropped out, people took 97% of their capsules, and there were no serious adverse reactions. Depression and anxiety scores improved more in the probiotic group on several scales, though not on one anxiety questionnaire (GAD-7).

How to read a gut-brain claim: the 2023 probiotic add-on pilot trial

Question	This study
Mouse or human?	Human: adults with diagnosed major depression already on antidepressants.
Correlation or cause?	Designed to test cause (randomized, placebo-controlled, double-blind), but it was a pilot trial whose main goals were feasibility: whether people would stick with it and tolerate it, plus rough effect estimates to plan a larger trial.
How many?	49 people analyzed (24 probiotic, 25 placebo). Too few to prove the probiotic works.
How long?	8 weeks. Nothing about long-term effects.
Who paid for it?	A UK Medical Research Council industrial PhD studentship with ADM Protexin, the probiotic's maker, as industry partner, plus a charitable donor. The paper says the funders had no role in design, analysis, or publication.
Is something being sold?	Yes. The probiotic is a commercial product, its maker co-funded the work, and the first author was also affiliated with the company.

The conclusion: this is a careful, honest small trial, and its authors described the results as "promising" and called for a definitive trial, not as proof. It supports running a bigger study. It does **not** show that this product, or probiotics in general, treats depression, and it says nothing about teens or about people not already on medicine. The company link doesn't make the results wrong; it's a fact a careful reader notes.

If you're going through this

If you live with IBS, IBD, anxiety, or depression, it's exhausting to be told by ads and relatives that a capsule will fix you, and it can feel like your fault when it doesn't. It isn't. Your treatment plan was built from much stronger evidence than a supplement label. If you're curious about a probiotic, bring the exact product to your doctor or dietitian and ask what's known about that strain for your condition, and never stop or swap a prescribed medicine for a supplement on your own.

At the Bedside: A Parent's Question in the NICU

Meet the patient (fictional)

Amara was born 10 weeks early and is 2 weeks old, growing slowly in the neonatal intensive care unit (NICU). Her mother, Grace, has been reading online parent groups, where several posts say probiotics "protect preemies' guts." Grace brings a bottle of a probiotic supplement from a store and asks the nurse whether she can mix some into Amara's milk.

What the doctor checks: The neonatologist (a doctor for newborns) listens to Grace's concerns and reviews Amara's history: how early she was born, her weight, how her feeding is going, any signs of infection, and whether she has a central line (a thin tube into a large vein). The doctor also looks at the bottle Grace brought: it's a dietary supplement, sold without FDA review, with a multi-strain "blend" and no strain codes.

Connecting the signals: Preterm babies are at risk of necrotizing enterocolitis, a serious inflammation of the gut, and researchers have studied whether certain probiotics lower that risk. But a premature baby's gut lining and immune system are still immature, so live microbes can occasionally get into the bloodstream and cause an infection. A product that hasn't been tested to drug standards might also contain organisms that aren't on the label.

Diagnosis: Prematurity with a family question about probiotic use. (There's no new disease; the "diagnosis" here is a benefit-risk decision.)

Why it happens: This chapter's probiotic safety section explains the core issue: probiotics are low-risk for most healthy people, but risk rises for people whose barriers and immune defenses aren't fully working. In October 2023, the FDA reported that probiotic products given to hospitalized preterm infants contributed to invasive disease, including one death, and said no probiotic is approved as a drug for infants.

The mind-body side: NICU parents often feel powerless, and giving a probiotic can feel like one thing they can do. The care team treats Grace's question as loving and reasonable, not foolish. They explain the risks, invite her to be part of decisions, and point her toward things that are within her control and supported by the team, such as skin-to-skin holding when Amara is stable and help with providing breast milk if she chooses. A NICU social worker or parent support group can help with the stress.

Treatment today: The team explains that hospital NICUs make their own policies about probiotics, weighing studies like those behind the 2020 AGA guideline against the 2023 FDA warning, and that no parent should add a store-bought supplement to a premature baby's feeds. The American Academy of Pediatrics, in a 2021 clinical report, said current evidence does not support giving probiotics routinely to all preterm infants, especially babies who weighed less than 1,000 grams at birth. Amara's care continues with standard NICU support: careful feeding, monitoring for infection and gut problems, and growth tracking.

What's new in research: A 2023 Cochrane review by Sharif and colleagues pooled 60 randomized trials with 11,156 very preterm or very low birth weight babies. Probiotics may lower the risk of necrotizing enterocolitis (low-certainty evidence) and probably lower the risk of death slightly (moderate-certainty evidence). But most trials were small, the products differed, and for the most premature and smallest babies the review found little or no clear effect. Researchers continue to study specific, well-characterized strains made to strict

manufacturing standards. In its 2023 statement, the FDA said that for a probiotic to be lawfully marketed as a drug or biological product for infants, it would need FDA approval based on evidence of safety and effectiveness. **Evidence grade: Moderate for a benefit in very preterm babies, but not settled for routine use.** Many human trials point toward fewer cases of necrotizing enterocolitis, but certainty is low to moderate, results vary by strain and setting, serious infections have been documented, and no probiotic is approved as a drug for infants.

Your turn: reason through a variation

Grace's nephew, Kofi, is 15 and getting chemotherapy for leukemia. A relative suggests a probiotic to help with his diarrhea. What should the family keep in mind?

Answer: Chemotherapy can weaken the immune system, which puts Kofi in the higher-risk group that NCCIH describes, where live microbes are more likely to cause infections. NCCIH also reports that a 2018 review of 12 studies found the evidence for probiotics preventing or treating chemotherapy-related diarrhea was inconclusive. So the possible benefit is uncertain and the risk is higher than for a healthy teen. The family should show the exact product to Kofi's oncology team before giving it, and follow their advice.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Probiotics are regulated like medicines, so the FDA has checked that they work.
Reality: Most probiotics in the US are sold as dietary supplements. Under a 1994 law, the FDA does not approve supplements before they're sold, and companies are responsible for their own safety and labels. Only a probiotic marketed to treat a disease must go through drug trials and FDA approval.

Myth: More CFUs means a better probiotic.
Reality: What matters is the specific strain, at the dose shown to work in a study, for the condition you care about. A huge CFU number of an untested strain is just untested at a higher amount, and counts printed "at time of manufacture" may overstate how many microbes are still alive.

Myth: If a probiotic worked in mice, it works in people.
Reality: The strain *L. rhamnosus* JB-1 reduced anxiety-like behavior in mice in 2011, but in a 2017 trial of 29 healthy men, it did nothing measurable for stress, mood, or thinking. Mouse results are a starting point, not proof.

Myth: "Psychobiotics" are an approved treatment for anxiety or depression.
Reality: "Psychobiotic" is a research term coined in 2013. It's not an approved product category, and no probiotic is FDA-approved to treat any mental health condition.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Clinically proven psychobiotic! 50 billion CFU of our exclusive Lactobacillus blend for calm, focus, and mood."

Grade: Hype. "Psychobiotic" is a research term, not an approved category, and "clinically proven" means nothing unless the specific strains were tested in well-designed human trials. A "Lactobacillus blend" gives no strain codes, so you can't match it to any study, and strain specificity means results don't transfer between strains. A large CFU count doesn't make up for missing evidence. A careful version would say: "Some specific probiotic strains are being studied for mood, with mixed and preliminary results in human trials. This product's strains have not been tested for that."

2. Predict: Sam reads that a new probiotic strain reduced anxiety-like behavior in mice whose vagus nerves were intact, but not in mice whose vagus nerves were cut. He wonders what a trial of the same strain in healthy teens would find. What would you predict, and why?

The most likely result is a small effect or no measurable effect, though it can't be known without testing. The mouse experiment suggests the vagus nerve carries the signal in mice, but mouse findings often don't carry over to people, as with JB-1, which helped mice and then did nothing in healthy men. Healthy teens also have less anxiety to reduce than a specially anxious mouse strain. A good trial would be randomized and placebo-controlled with a primary outcome chosen in advance.

3. Explain: A meta-analysis of 12 probiotic trials found a significant improvement on the Beck Depression Inventory but not on three other depression scales. Explain why this result should be interpreted cautiously.

When you measure several outcomes, the chance that at least one looks significant by luck goes up, even if the treatment does nothing. Only one of four scales showed a benefit, and the two clinician-rated scales did not. Different trials also used different strains and people, so the result could reflect certain trials rather than probiotics in general. The authors themselves called for cautious interpretation.

4. Apply: Riya's grandmother wants to buy her a probiotic labeled "supports digestive health" to help her Crohn's disease. Using this chapter, what should Riya know before taking it?

The label is a structure-function claim that a supplement can make without FDA review; it doesn't mean the product treats Crohn's, and it isn't allowed to claim that. The AGA 2020 guideline recommends probiotics for Crohn's only within clinical trials. Riya also takes a biologic, which affects her immune system, so she should show the product to Dr. Alvarez before taking it. Her grandmother's care is real, and Riya can thank her while explaining that her doctor needs to check first.

5. Read the data. In a 2017 randomized, placebo-controlled crossover trial, Kelly and colleagues gave the probiotic strain *L. rhamnosus* JB-1 or a placebo to healthy men for 4 weeks each (8 weeks in total). Compare it with the earlier mouse study of the same strain (Bravo 2011):

Feature	Bravo et al., 2011	Kelly et al., 2017
Who	Mice (an anxious lab strain, per Kelly)	29 healthy men
Design	Probiotic vs control feeding; plus vagotomy experiment	Randomized, placebo-controlled crossover, 4 weeks per period (8 weeks total)
Stress hormone after stress	Lower with probiotic	No difference from placebo
Anxiety- or mood-related measures	Less anxiety- and depression-like behavior	No difference in mood, anxiety, stress, or sleep quality
Thinking and brain activity	GABA receptor changes in brain regions	No improvement in memory, attention, or EEG

5. What does this data show, and what can't it show?

It shows that a strain with clear effects in mice had no measurable effect in a small, well-controlled trial of healthy men. That's a replication failure across species. It can't show that JB-1 is useless for everyone: the human study was small (29 people), included only healthy men, and didn't test people with anxiety or depression, women, or teens. It also can't tell us whether a different dose or longer treatment would matter. A helpful follow-up would be a larger placebo-controlled trial of JB-1 in people with a diagnosed stress-related or anxiety disorder, with a primary outcome named in advance.

Exercises

Remember

1. Give the ISAPP definition of a probiotic in your own words, and name the three conditions it includes.

Answer

A probiotic is a live microbe that gives a health benefit when taken in a large enough amount. The three conditions: the microbes are alive, they are given in an adequate amount, and a health benefit has been shown.

1. What does a colony-forming unit count, and why are probiotic doses given in CFU?

Answer

It counts the microbes in a sample that are alive and able to multiply, because each one forms a visible colony on a lab dish. Doses use CFU because the definition of a probiotic requires live microbes, and dead ones don't form colonies.

Understand

1. Explain the difference between a prebiotic and a postbiotic, using the garden comparison.

Answer

A prebiotic is like fertilizer: a substance that certain microbes already in the gut use selectively, producing a health benefit. A postbiotic is like mulch made from old plants: a preparation of inactivated (non-living) microbes or their parts that gives a health benefit.

1. Explain why a probiotic trial should name its primary outcome before the results are known.

Answer

If researchers measure many outcomes, some will look significant by chance even if the treatment does nothing. Naming one primary outcome in advance prevents them from reporting whichever result happened to look best, so the main test of the treatment is fair.

Apply

1. Find a probiotic product label (online or in a store, without buying it). Using the table in Section 16.4, list what the label tells you and what it leaves out, and decide whether you could match it to a published study.
2. Using the Probiotic Trial Reader, run 20 trials at 20, 60, and 300 people per group (1 outcome, placebo on). Record the share of "impressive" results and the average reported effect for each. Describe the pattern and explain how it relates to small supplement studies in ads.

Analyze

1. Compare the Bravo 2011 mouse study and the Kelly 2017 human trial using all six questions from the claim box. Which question best explains why the results differ?

2. The Liu 2019, Asad 2025, and Pan 2025 meta-analyses reached different effect sizes for probiotics and depression. Analyze at least three reasons, from this chapter, that reviews of "the same" question can disagree.

Evaluate

1. A friend argues: "The FDA warned about probiotics for preterm babies, but the AGA suggested some strains for them, so the experts are just confused." Write a paragraph judging this argument. What does the disagreement actually reflect, and how should families and hospitals handle it?
2. Evaluate the Nikolova 2023 pilot trial as evidence. Would you call its result Strong, Moderate, Preliminary, or Hype for the claim "probiotics help people with depression who are already on antidepressants"? Defend your grade using the claim box.

Create

1. Design a trial that could fairly test whether a specific probiotic strain reduces test anxiety in high school students. Name your strain choice, groups, blinding, length, primary outcome, sample size reasoning, and how you would prevent publication bias.
2. Rewrite Dev's "Calm in a Capsule" post (Section 16.1) as an honest product description that would earn a fair Hype Meter grade. Keep it under 80 words.

Key Takeaways

- A probiotic is a live microbe given in adequate amounts with a demonstrated health benefit; prebiotics feed certain gut microbes, synbiotics combine the two, and postbiotics are inactivated microbes or their parts. Every definition requires a proven benefit.
- Most probiotics belong to the Lactobacillus (now split into 25 genera) and Bifidobacterium groups, but effects are strain specific: results from one strain and one condition don't carry over to others.
- A CFU count measures live microbes. More CFU isn't automatically better; what matters is the tested strain, at the tested dose, for the tested condition, counted at the end of shelf life.
- In the US, most probiotics are dietary supplements, which don't need FDA approval before sale and can't claim to treat disease. "Psychobiotic" is a research term from 2013, not an approved category.
- Probiotics are low-risk for most healthy people but riskier for people who are very ill, immunocompromised, or born early; in 2023 the FDA warned that probiotics given to hospitalized preterm infants caused serious infections, including a death.
- The JB-1 strain calmed mice but did nothing in healthy men, a classic replication failure. Evidence that probiotics treat depression or anxiety in people is Preliminary.

- To read trials, look for systematic reviews, effect sizes, a primary outcome set in advance, and signs of publication bias, and be wary of small trials that measured many outcomes.

You can read the back of the bottle now!



You've learned to check the strain, the dose, the regulation, and the trials behind any probiotic claim. Next, in Chapter 17, we'll look at gut-brain treatments that did earn FDA approval, from stool-based medicines to nerve stimulators, and how they got there.

Quiz: Probiotics, Prebiotics, and "Psychobiotics"

Test your understanding of Chapter 16. Choose the best answer, then click **Show Answer** to check.

Question 1

According to the ISAPP scientific definition, which of these is required for a product to be called a probiotic?

A. It must contain at least 50 billion colony-forming units.

B. It must contain live microorganisms, in adequate amounts, with a shown health benefit.

C. It must be approved by the FDA as a drug.

D. It must contain fiber that feeds gut bacteria.

Show Answer

The correct answer is **B**. The ISAPP (2014) definition is "live microorganisms that, when given in adequate amounts, confer a health benefit on the host." Option D describes a prebiotic, which is food for microbes rather than live microbes. No specific CFU number or FDA approval is part of the definition.

Concept Tested: Probiotic **Bloom's Level:** Remember

Question 2

A product contains heat-killed bacterial cells and their parts, and a health benefit has been shown. Under the ISAPP definitions, what is it?

A. A probiotic

B. A prebiotic

C. A synbiotic

D. A postbiotic

Show Answer

The correct answer is **D**. A postbiotic is "a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host." It can't be a probiotic, because probiotics must be alive. A synbiotic combines live microbes with a substance microbes use.

Concept Tested: Postbiotic **Bloom's Level:** Remember

Question 3

Under the 1994 Dietary Supplement Health and Education Act (DSHEA), which statement is true about probiotics sold as dietary supplements in the US?

A. The FDA does not approve them for safety or effectiveness before they are sold.

B. The FDA tests every bottle before it reaches stores.

C. They must show benefit in two clinical trials before sale.

D. They are allowed to claim they cure diseases if the company believes it.

Show Answer

The correct answer is **A**. Under DSHEA, the FDA does not have the authority to approve dietary supplements before they are marketed; companies are responsible for safety and labeling, and the FDA can act after a product is on the market. Option D is wrong: supplements may make structure-function claims but cannot claim to treat, cure, or prevent a disease.

Concept Tested: Dietary Supplement Regulation **Bloom's Level:** Remember

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Question 4

Why can't the results of a trial on one *Lactobacillus* strain be assumed to apply to a different *Lactobacillus* strain?

A. Because only one Lactobacillus strain can survive in the human gut

B. Because the FDA approves each strain separately before sale

C. Because probiotic effects are strain specific and also depend on the condition being treated

D. Because Lactobacillus strains all have the same effect, so testing a second one is unnecessary

Show Answer

The correct answer is **C**. A 2018 review of 228 trials found that probiotic efficacy depends on both the strain and the disease, and NCCIH says one strain's benefit doesn't prove another works. Option B is wrong because most probiotics are supplements that the FDA doesn't approve before sale.

Concept Tested: Strain Specificity **Bloom's Level:** Understand

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Question 5

A probiotic label lists "20 billion CFU at time of manufacture." Why might this overstate what you actually get?

A. CFU counts dead bacteria as well as live ones.

B. Many strains lose live cells during storage, so fewer may be alive by the time you take it.

C. The FDA requires labels to round CFU numbers up.

D. CFU measures the weight of the capsule, not the number of microbes.

Show Answer

The correct answer is **B**. ISAPP's label guide explains that most strains lose live cells over their shelf life, so a count at manufacture can be much higher than at the end of shelf life. Option A is backwards: CFU counts only microbes alive enough to form colonies.

Concept Tested: Colony-Forming Unit **Bloom's Level:** Understand

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Question 6

In a 2011 study, the strain *L. rhamnosus* JB-1 reduced anxiety-like behavior in mice, but in a 2017 trial of 29 healthy men it did nothing measurable. What does this pair of studies best illustrate?

A. A replication failure across species, showing a mouse result may not carry over to people

B. Proof that the mouse study was faked

C. Proof that probiotics can never affect the brain

D. Publication bias, because the human study was never published

Show Answer

The correct answer is **A**. When a later study tests the same idea and doesn't find the original result, that's a replication failure. It doesn't prove fraud or that probiotics can never matter; the human study was small and used healthy men, not people with anxiety. Option D is wrong because the human study was published.

Concept Tested: Replication Failure **Bloom's Level:** Understand

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Question 7

A meta-analysis of probiotic trials found improvement on one depression questionnaire but not on three others. A news story says, "Probiotics proven to reduce depression!" What is the best response?

A. Accept it, because any significant result counts as proof.

B. Reject probiotics completely, because three scales showed no difference.

C. Ignore the questionnaires and look only at the number of participants.

D. Be cautious: with several outcomes, one positive result could be chance, so the evidence is mixed.

Show Answer

The correct answer is **D**. When many outcomes are measured, the chance that at least one looks significant by luck rises, which is why trials name a primary outcome in advance. The Rahmannia 2024 review's authors urged cautious interpretation. Option B overcorrects: mixed results mean uncertainty, not proof of no effect.

Concept Tested: Primary Outcome **Bloom's Level:** Apply

Question 8

Sixteen-year-old Malia is getting chemotherapy, and a relative wants her to start a store-bought probiotic. Based on the chapter, what is the most accurate advice?

A. It is safe, because probiotics are natural.

B. Her oncology team should review the exact product first, because people with weakened immune systems face higher risk from live microbes.

C. She should take a double dose to make sure enough bacteria survive.

D. Probiotics are only risky for adults over 65.

Show Answer

The correct answer is **B**. NCCIH says the risk of harm from probiotics is greater in people with severe illness or weakened immune systems, which can include people on chemotherapy. Option A is the "natural means safe" myth, and the book never recommends doses.

Concept Tested: Probiotic Safety **Bloom's Level:** Apply

Question 9

In a 2008 study, published journal articles made about 94% of antidepressant trials look positive, but FDA records showed about 51% were positive. What explains the gap?

A. Publication bias: negative trials were often unpublished or reported as if positive.

B. The FDA made errors in judging the trials.

C. The drugs became more effective after the trials ended.

D. Journals only publish trials with more than 1,000 people.

Show Answer

The correct answer is **A**. Turner and colleagues found that 22 negative or questionable trials were never published and 11 were published in a way that conveyed a positive result, which made the drugs' effect look about 32% bigger overall. That pattern is publication bias. Nothing in the study suggests FDA errors.

Concept Tested: Publication Bias **Bloom's Level:** Analyze

Question 10

Three meta-analyses of probiotics (and related treatments) for depression report effect sizes of about 0.24, 0.26, and 0.96. Which explanation from the chapter best accounts for the difference?

A. One of the reviews must have made a math mistake.

B. Effect sizes always triple when more trials are added.

C. Larger effect sizes always come from the best-designed reviews.

D. The reviews included different trials, people, strains, and lengths of treatment, and the trials disagreed a lot.

Show Answer

The correct answer is **D**. The reviews pooled different sets of trials: for example, Asad 2025 included only people with a diagnosis and reported high heterogeneity, while Liu 2019 also included people without a diagnosis (and found a bigger effect in clinical samples). Strain specificity means "probiotics" can mean different products in each review. Option C is wrong because a bigger effect size does not mean better design.

Concept Tested: Systematic Review **Bloom's Level:** Analyze

Chapter 17: Medicine for the Gut-Brain Axis

Summary

Some gut-brain treatments have moved from the lab into real medicine. This chapter explains how fecal microbiota transplant became a lifesaving treatment for repeat *C. difficile* infections, and how two microbiome medicines made from donated stool earned FDA approval in 2022 and 2023. It follows vagus nerve stimulation from its approval for epilepsy in 1997 to depression in 2005, stroke rehabilitation in 2021, and rheumatoid arthritis in 2025, and contrasts those devices with consumer "vagus" gadgets. It explains why doctors prescribe low doses of old antidepressants for IBS pain. Along the way, you'll learn how treatments get approved (and how "approved," "cleared," and "off-label" differ), how doctors weigh benefits against risks, and how patients and doctors make these choices together.

Concepts Covered

1. C. difficile Infection
2. Fecal Microbiota Transplant
3. Live Biotherapeutic Product
4. FDA Approval
5. Clinical Trial Phases
6. Off-Label Use
7. Benefit-Risk Balance
8. Vagus Nerve Stimulation
9. Implanted VNS Device
10. Noninvasive VNS
11. Inflammatory Reflex
12. Bioelectronic Medicine
13. Consumer Wellness Device
14. Tricyclic Antidepressant
15. Shared Decision-Making
16. Precision Medicine

Prerequisites

- Chapter 2: The Vagus Highway (afferent and efferent vagus fibers)
- Chapter 3: Meet the Microbiome (dysbiosis, antibiotic disruption)
- Chapter 4: The Immune System as a Sense Organ (cytokines and inflammation)
- Chapter 9: Inflammatory Bowel Disease (biologic therapy, remission)
- Chapter 10: IBS and Disorders of Gut-Brain Interaction (gut-brain neuromodulators, placebo response)
- Chapter 16: Probiotics, Prebiotics, and "Psychobiotics" (supplement regulation, trial reading)

From the lab to the pharmacy



In the last chapter, most products had never been checked by anyone before they were sold. This chapter is about treatments that went through the full gauntlet of trials and FDA review, including one that stimulates my home nerve with electricity. Knowing exactly what each one is approved for, and what it isn't, will protect you from a lot of confusing headlines.

17.1 "Wait, They Transplant *What*?"

Riya is in Dr. Alvarez's office for her regular checkup. Her Crohn's disease has been quiet for months, and her biologic injections are working. But she has two questions saved on her phone. The first came from a video her cousin sent: a woman described how a bacterial infection called *C. difficile* kept coming back after every round of antibiotics, three times in one year, until doctors treated her with a "fecal transplant." She said it gave her life back. "Is that real?" Riya asks. "And could a fecal transplant fix my Crohn's?"

Her second question came from Sam, who had seen an ad for a $300 ear clip that "activates your vagus nerve" to melt away anxiety. Riya had also read that doctors implant vagus nerve stimulators in some patients. "Are those the same thing?" (Riya, Sam, and Dr. Alvarez are fictional.)

Dr. Alvarez smiles. "Great questions. One of those has FDA-approved versions and works remarkably well, but only for one specific infection. One is still being tested. And one is a gadget that hasn't been shown to do what it claims." By the end of this chapter, you'll be able to sort them yourself.

17.2 When Antibiotics Clear the Garden: C. difficile Infection

Imagine a lawn so thick with healthy grass that weeds can't find a spot to grow. Now spray it with weed killer that also kills most of the grass. In the bare patches, the toughest weed on the block moves in and takes over. Even if you spray again, the weed often comes back, because the grass that used to crowd it out is still missing.

That's roughly what happens in one of the most common hospital infections in the United States. **C. difficile infection** (CDI) is an infection of the colon by the bacterium *Clostridioides difficile* (often shortened to *C. diff*), which causes diarrhea and inflammation of the colon and can be life-threatening. It most often happens during or soon after a course of antibiotics, which can wipe out many of the normal gut bacteria that usually keep *C. diff* in check (the "antibiotic disruption" from Chapter 3).

According to the Centers for Disease Control and Prevention (CDC):

- *C. diff* causes almost **half a million infections** in the United States each year.
- People are up to **10 times more likely** to get it while taking an antibiotic, and the risk stays higher for about a month after.
- Symptoms include diarrhea, fever, stomach pain or tenderness, loss of appetite, and nausea.
- Risk is higher for adults 65 and older, people in hospitals and nursing homes, people with weakened immune systems, and people who have had *C. diff* before.

The FDA, in its 2023 announcement of a new treatment, said *C. diff* is associated with **15,000 to 30,000 deaths** in the United States each year.

The hardest part is that it keeps coming back. A 2023 Cochrane review notes that *C. diff* can cause recurrent infections in nearly a third of people who get it. The FDA explains that the risk of another recurrence rises with each infection, while treatment options shrink. Doctors needed a way to replant the lawn.

17.3 Replanting the Garden: Fecal Microbiota Transplant

The idea sounds strange at first: if the problem is missing healthy gut bacteria, give the patient healthy gut bacteria from someone else. And the richest source of a healthy person's gut bacteria is their stool.

A **fecal microbiota transplant** (FMT) is a procedure in which stool from a carefully screened healthy donor, containing that person's gut microbes, is delivered into a patient's digestive tract to restore a healthier microbial community. It can be given through a colonoscope (a flexible tube with a camera, passed into the colon), an enema, a tube through the nose into the small intestine, or capsules.

The trial that changed medicine

Doctors had tried FMT before, but they wanted proof from a randomized trial. In 2013, a team in Amsterdam led by van Nood published the first randomized controlled trial of FMT for recurrent *C. diff* in the *New England Journal of Medicine*. Adults with recurrent infection were randomly assigned to one of three groups:

Group	Resolution of C. diff without relapse (10 weeks)
Short antibiotic course, bowel cleanse, then donor-stool infusion	13 of 16 (81%) after the first infusion
Standard antibiotic (vancomycin) alone	4 of 13 (31%)
Vancomycin plus bowel cleanse	3 of 13 (23%)

The difference was so large that the study was stopped early, after an interim check showed the donor-stool group was doing far better. Of the 3 people whose infection wasn't cleared by the first infusion, 2 were cured after a second infusion from a different donor.

This was a small trial (42 people in total), but the effect was huge, and later trials agreed. A 2023 Cochrane systematic review pooled 6 randomized trials with 320 adults whose immune systems were working normally. FMT roughly doubled the chance that recurrent *C. diff* cleared up compared with control treatments (risk ratio 1.92), and the reviewers rated this moderate-certainty evidence. They calculated that about **3 people** need to be treated with FMT for one additional person to be cured (a "number needed to treat" of 3, which is very good). The review couldn't reach firm conclusions on safety, because serious harmful events were rare in these small trials, and it couldn't say much about people with weakened immune systems, who were mostly excluded.

Why screening matters, and why DIY FMT is dangerous

Stool can also carry viruses, parasites, and antibiotic-resistant germs, so medical FMT uses screened donors and tested stool.

Even screening can miss something. In 2019, doctors at Massachusetts General Hospital reported in the *New England Journal of Medicine* that two patients in two different FMT clinical trials developed bloodstream infections with a drug-resistant strain of *E. coli*. Genetic testing traced both infections to the same stool donor, and one of the patients died. The doctors who reported the cases called for enhanced donor screening. A homemade "FMT" with untested stool from a friend or relative is far riskier. Do-it-yourself FMT is unsafe.

"It's just bacteria" is not a safety plan



The same thing that makes FMT powerful, transferring a whole living community, is what makes it risky. Medical FMT works because of donor screening, stool testing, and follow-up; a homemade version skips every one of those safeguards.

17.4 From Stool to Medicine: Live Biotherapeutic Products

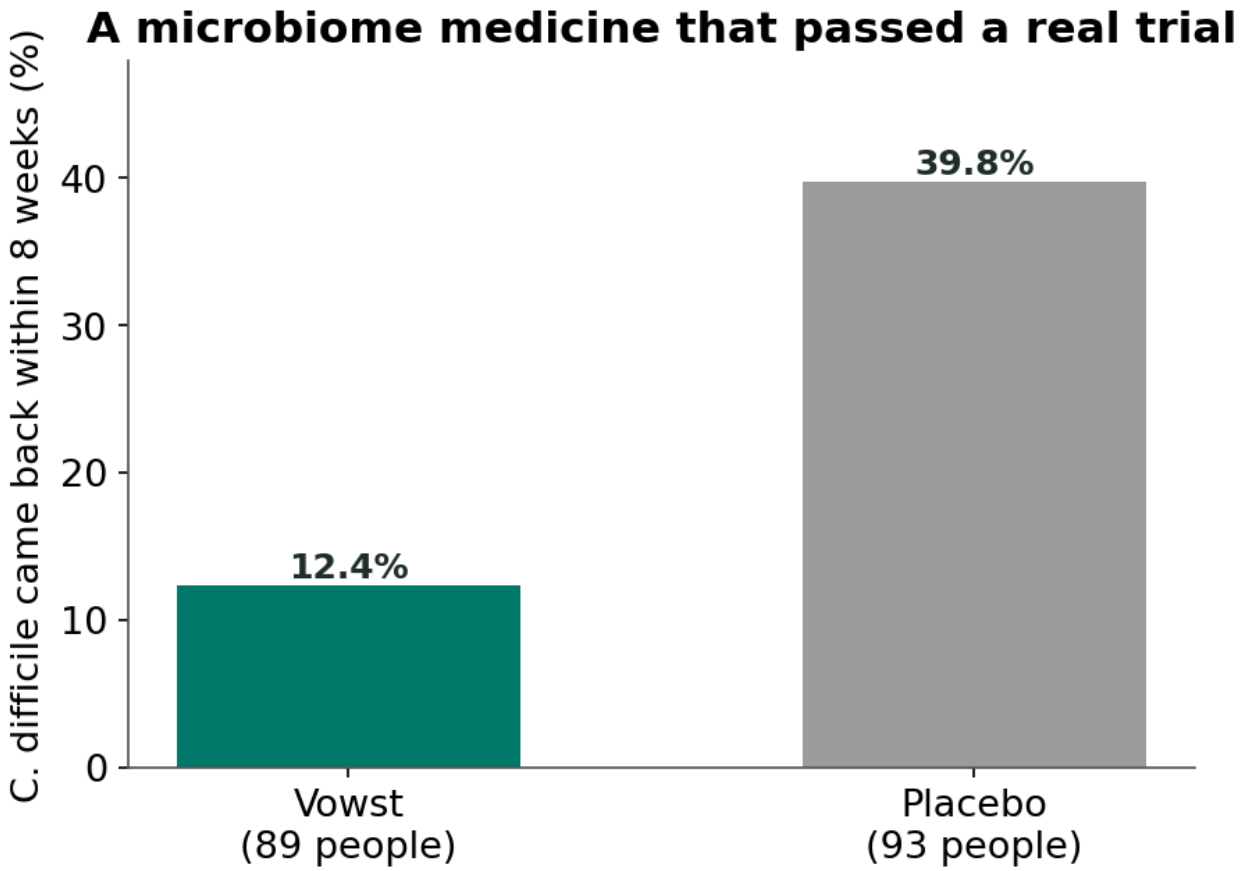
FMT from a hospital stool bank works, but every batch comes from a different person. Medicines are supposed to be consistent, so companies set out to turn FMT into a standardized product that could earn FDA approval.

A **live biotherapeutic product** (LBP) is a medicine that contains live microorganisms, such as bacteria, and is meant to prevent, treat, or cure a disease. According to a 2020 review by Cordaillat-Simmons and colleagues, the FDA first proposed this category in a 2010 draft guidance. The key difference from the probiotics in Chapter 16 is regulation: an LBP is reviewed like a drug or biologic. Its maker must prove in clinical trials that it is safe and effective for a specific disease and must meet strict manufacturing and testing standards before it can be sold.

As of October 2026, two products made from donated human stool have been FDA approved, both for the same narrow purpose:

Product	FDA approval date	How it's given	Approved use
Rebyota (fecal microbiota, live-jslm)	November 30, 2022	Single rectal dose	Prevent *C. diff* infection from coming back in adults 18 and older, after antibiotic treatment for recurrent infection
Vowst (fecal microbiota spores, live-brpk)	April 26, 2023	Oral capsules, taken over 3 days	Same: prevent recurrence in adults 18 and older after antibiotic treatment for recurrent infection

Rebyota, made by Ferring Pharmaceuticals, was the first FDA-approved fecal microbiota product. Vowst, developed by Seres Therapeutics and sold to Nestlé Health Science in 2024, was the first one taken by mouth. In the trial the FDA described when it approved Vowst, 89 people received Vowst and 93 received a placebo after finishing antibiotics. Over the next 8 weeks, *C. diff* came back in **12.4%** of the Vowst group compared with **39.8%** of the placebo group.



Source: US FDA, April 26, 2023 approval announcement (ECOSPOR III trial). Adults with recurrent C. difficile infection, after antibiotic treatment.

Read the "approved use" column carefully, because the limits matter:

- **Prevention of recurrence, not treatment.** Both are given *after* antibiotics have treated a recurrent infection, to stop it from returning. Neither is approved to treat an active infection or a first episode.
- **Adults only.** Both are approved for people 18 and older.
- **Only *C. diff*.** Neither is approved for IBD, IBS, autism, depression, or any other condition.

The FDA also notes that because Vowst is made from human stool, it may carry a risk of transmitting infectious agents even though donors and stool are tested.

Same idea, different rules



A probiotic supplement and an approved live biotherapeutic product both contain live microbes, but only one had to prove in trials that it works for a disease before it reached patients. When I want to know how much to trust a microbe product, I ask which set of rules it followed.

17.5 How a Treatment Earns Approval

Approval for drugs and biologics

FDA approval is the US Food and Drug Administration's decision, based on evidence the company submits, that a drug, biologic, or high-risk device is safe and effective for a specific intended use. The FDA explains that "safe" doesn't mean a treatment has no side effects. It means the FDA has decided that, for that particular use, the benefits outweigh the possible risks. Approval comes with official labeling that lists the exact conditions the treatment is approved for.

That last part is the key to reading headlines. **Approval is always for a specific use.** A drug approved for one type of cancer is not approved for another type, and a device approved for epilepsy is not approved for anxiety.

The phases of clinical trials

Before approval, a new drug usually goes through **clinical trial phases**, a series of increasingly large studies in people that test first safety, then whether the treatment works, then how it compares at a large scale, with monitoring continuing after approval. The FDA describes them like this:

Phase	Who takes part	Typical length	Main purpose	Share of drugs that move on
Phase 1	About 20 to 100 healthy volunteers or people with the condition	Several months	Safety and dosage	About 70%
Phase 2	Up to several hundred people with the condition	Several months to 2 years	Whether it works, and side effects	About 33%
Phase 3	About 300 to 3,000 people with the condition	1 to 4 years	Confirm it works, watch for side effects	About 25 to 30%
Phase 4	Several thousand people	After approval	Ongoing safety monitoring	(already approved)

Most treatments drop out along the way, which is why "a new study shows promise" is very different from "approved."

Devices: approval, clearance, and authorization

Medical devices follow different paths depending on their risk, and the words matter:

Pathway	What the FDA decides	Word to use	Example in this chapter
Premarket approval (PMA)	The device has enough scientific evidence of safety and effectiveness; FDA calls this its most stringent device review, used for the highest-risk (Class III) devices	**Approved**	Implanted vagus nerve stimulators
De Novo	A new type of device with no existing equivalent, for which general or special controls can reasonably assure safety and effectiveness	**Authorized** (granted)	gammaCore for cluster headache (2017)
510(k)	The device is "substantially equivalent" to a device already legally on the market	**Cleared**	gammaCore expansion to migraine (2018)

"Cleared" and "authorized" are real FDA decisions, but they are not the same as "approved."

Off-label use

Once a drug is approved, doctors may sometimes prescribe it for a different condition. **Off-label use** is the use of an FDA-approved drug for a condition, dose, or form that is not listed in its official labeling. The FDA explains that, once a drug is approved, health care providers generally may prescribe it for an unapproved use when they judge that it's medically appropriate for their patient, for example when no approved drug exists for a condition, or approved treatments haven't worked. The FDA is also clear about the trade-off: for the off-label use, it has not determined that the drug is safe and effective. Off-label use can be backed by good research (see Section 17.9), but it should be a thoughtful choice made with a doctor.

Benefit-risk balance

Every treatment decision, by the FDA or by a patient and doctor, comes down to a **benefit-risk balance**: weighing how much a treatment is likely to help against how likely and how serious its harms are, for a particular person and a particular condition. The same treatment can have a great balance for one person and a poor one for another.

FMT shows how this works. For an adult whose *C. diff* keeps coming back despite antibiotics, the benefit is large (roughly 3 people treated for one extra cure), so a small risk of infection is worth taking. For a healthy person who wants to "optimize" their gut, there's no proven benefit, so any risk tips the balance the wrong way.

17.6 FMT Beyond C. diff: Hope, Hype, and Ongoing Trials

If FMT works so well for *C. diff*, why not for other conditions linked to the microbiome? Here's where the research stood as of 2026.

Ulcerative colitis. A 2023 Cochrane review of 12 randomized trials with 550 participants found that FMT *may* help some people with active ulcerative colitis reach clinical remission, but rated the evidence low certainty. Results for endoscopic remission (healing seen through a scope) were uncertain, and the evidence for keeping people in remission was very uncertain. FMT for ulcerative colitis is **experimental**, not approved.

Crohn's disease. The same review found the evidence for Crohn's disease very uncertain, with few studies. That's the answer to Riya's question: FMT for Crohn's is a research question, not a treatment her doctor can prescribe.

Autism. A 2017 study by Kang and colleagues gave 18 autistic children, aged 7 to 16, an intensive microbiota transfer protocol (antibiotics, a bowel cleanse, then many weeks of donor microbes). Their gastrointestinal symptoms, such as constipation, diarrhea, and stomach pain, improved by about 80% on a symptom scale, and the researchers also reported changes on behavior measures. But the study was **open-label**, meaning everyone knew they were getting the treatment, and it had **no placebo group**, so it can't show the treatment caused the changes. Gut problems in autistic children are real health problems worth treating on their own terms, and this study is a reason for further research on them. It is not proof of a treatment, and autism itself is a neurodevelopmental difference, not a disease to be cured by changing the microbiome (see Chapter 13).

Parkinson's disease. Here the placebo-controlled trials disagree. A 2024 Belgian trial (GUT-PARFECT) of 46 people with early Parkinson's found a mild improvement in movement scores after 12 months with donor stool compared with the patients' own stool. But a 2024 Finnish trial of 48 people found FMT was safe and did not offer clinically meaningful improvements, and a 2026 Polish trial of 59 people found that a single FMT did not change movement symptoms, though some non-movement symptoms improved at certain time points. Mixed results from small trials mean FMT for Parkinson's remains **experimental**.

Condition	Best evidence so far (as of 2026)	Status
Recurrent *C. diff*	Several randomized trials and a Cochrane review; two approved products	Approved products and standard care
Ulcerative colitis	Cochrane review, low-certainty benefit	Experimental
Crohn's disease	Very uncertain	Experimental
Autism	Small open-label studies, no placebo group	Experimental (not a cure)
Parkinson's disease	Small placebo-controlled trials with mixed results	Experimental

Hype Meter: "Poop transplants cure autism and Parkinson's"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. For autism, the best-known study had 18 children, no placebo group, and participants who knew they were treated, so it can't show cause. For Parkinson's, three small placebo-controlled trials found a mild benefit in one and no meaningful motor benefit in two. No FMT product is approved for either condition, and "cure" isn't supported by any study. **What would change the grade:** Large, placebo-controlled, repeated trials showing clear, lasting benefits would move specific, carefully worded claims (such as "improves GI symptoms in some autistic children") toward Preliminary or Moderate. "Cure" would still not fit.

17.7 Treating the Body Through Its Wiring: Vagus Nerve Stimulation

Now to Riya's second question. Remember from Chapter 2 that the vagus nerve is a two-way highway between the brainstem and the organs of the chest and abdomen, and that most of its fibers carry signals up to the brain. If you could send small electrical pulses along that highway, could you change what the brain or body does?

Vagus nerve stimulation (VNS) is a treatment that delivers mild electrical pulses to the vagus nerve, either through a device implanted under the skin or through a handheld device placed on the skin, to change nerve signaling to the brain or the body. Think of it like tapping out a signal on a telegraph line that already runs between two cities. You aren't building new wiring; you're sending a message along wiring that's already there.

Implanted devices: four different approvals

An **implanted VNS device** is a small pulse generator placed under the skin by a surgeon and connected to the vagus nerve in the neck, which delivers programmed electrical pulses on a schedule. Different implanted devices have been approved for four very different conditions:

Year approved	Device	Approved for	Notes
1997 (July 16)	VNS Therapy System (originally the NeuroCybernetic Prosthesis, now made by LivaNova)	Add-on treatment for drug-resistant partial-onset epilepsy	The first FDA-approved VNS device

Year approved	Device	Approved for	Notes
2005 (July 15)	VNS Therapy System (new approved use)	Add-on, long-term treatment of chronic or recurrent depression in adults 18 and older in a major depressive episode who have not responded well to 4 or more adequate antidepressant treatments	For treatment-resistant depression only
2021 (August 27)	Vivistim System	Use during rehabilitation therapy to reduce arm movement problems in people with chronic ischemic stroke and moderate to severe arm weakness	Stimulates the vagus nerve during rehabilitation exercises, not on a daily schedule
2025 (July 30)	SetPoint System	Adults with moderately to severely active rheumatoid arthritis who did not respond well to, lost response to, or could not tolerate one or more biologic or targeted synthetic drugs	Stimulates the left vagus nerve for 1 minute once a day

Notice how specific each approval is. The depression approval is not for anyone with depression; it's an add-on for adults whose depression has resisted at least four other treatments. And as of October 2026, **no VNS device is approved for Crohn's disease, IBS, or anxiety.** (One prescription ear stimulator has a narrower FDA authorization for IBS pain in 11- to 18-year-olds; Section 17.8 explains it.)

Hype Meter: "Vagus nerve stimulation is FDA approved for depression"

Strong | Moderate | Preliminary | Hype

Verdict: Strong, with fine print. FDA records show that in July 2005 the implanted VNS Therapy System was approved as an add-on, long-term treatment for adults with chronic or recurrent depression who haven't responded to 4 or more adequate antidepressant treatments. The approval fact is solid. How well VNS works for depression is less clear-cut than the approval itself, so the evidence for its benefit is better described as Moderate, and it is not a first-choice treatment. **What would change the grade:** The approval fact won't change unless the FDA changes the label. A version of the claim that drops the fine print ("VNS treats depression," implying anyone, any device) would earn a lower grade.

The inflammatory reflex

Why would a nerve stimulator help arthritis, a disease of the immune system? The answer comes from a discovery about how nerves and immune cells talk to each other.

Your body has reflexes for many things: pull your hand from a hot stove, and your spinal cord acts before you think. In 2002, Kevin Tracey, a scientist in New York, described a reflex for inflammation. The **inflammatory reflex** is a nerve circuit in which the brain senses inflammation (partly through incoming vagus signals) and responds by sending signals back out, largely through the vagus nerve, that calm the immune system's release of inflammatory chemicals such as cytokines (from Chapter 4). Tracey's key point was that the nervous system regulates inflammation in real time, the way it controls heart rate, and that neurons using the chemical messenger acetylcholine can shut down acute inflammation. Much of the detailed evidence for this circuit comes from animal studies.

That idea led to a new field. **Bioelectronic medicine** is an approach to treatment that uses electrical stimulation of nerves, instead of or alongside drugs, to change how organs or the immune system work. The SetPoint System is the first device the FDA has approved to treat rheumatoid arthritis, an autoimmune disease, by stimulating the vagus nerve.

How strong is the evidence? SetPoint's first human pilot study, published in 2020 by Genovese and colleagues, enrolled just 14 patients and was funded by the company. The larger RESET-RA trial, summarized by the FDA, randomly assigned 242 adults to active stimulation or sham stimulation (an implanted device that wasn't turned on). After 12 weeks, 35.2% of the active group versus 24.2% of the sham group had at least a 20% improvement on a standard arthritis scale (ACR20). That's a real but modest difference from one sham-controlled trial. The full peer-reviewed results appeared in *Nature Medicine* in December 2025 (Tesser and colleagues) and reported the same 12-week numbers. After 12 weeks, everyone's device was switched on, and by 12 months 52.8% of the people who completed the study met the ACR20 mark. That later number is harder to interpret, because there was no longer a sham group to compare against, so some of the improvement could come from expectations or from the disease changing on its own. The trial was sponsored by SetPoint Medical, and several authors work for the company. Serious problems related to the device or surgery occurred in 1.6% of patients, all around the time of surgery, and all resolved.

What about Crohn's disease?

The same idea makes researchers wonder about Crohn's, another inflammatory disease. In a 2016 pilot study, Bonaz and colleagues in France implanted vagus nerve stimulators in 7 patients with active Crohn's disease and followed them for 6 months. Two were taken out of the study at 3 months because their disease got worse; the other 5 moved toward remission. A second small study, published in 2023, treated 16 patients with drug-resistant Crohn's disease; D'Haens and colleagues reported lower disease activity and inflammation markers, but it was also open-label, with no comparison group. Two small studies without control groups are a starting point, not proof. VNS for Crohn's is **experimental**. Dr. Alvarez tells Riya it's an interesting area to watch, and that her biologic, which has strong evidence behind it, is doing its job.

17.8 Handheld Stimulators and Wellness Gadgets

Implanted devices require surgery. Could you stimulate the vagus nerve from outside the body?

Noninvasive VNS is vagus nerve stimulation delivered through the skin, without surgery, using a handheld or wearable device placed on the neck or the ear. The best-known medical example is gammaCore, a handheld device held against the side of the neck. The FDA's records show:

- **April 14, 2017:** The FDA granted a De Novo authorization for gammaCore for the acute treatment of pain from episodic cluster headache in adults.
- **January 23, 2018:** A 510(k) clearance added the acute treatment of pain from migraine headache in adults.
- **February 12, 2021:** A later 510(k) clearance extended migraine treatment to teens 12 to 17. (Other clearances added more headache uses.)

These are FDA **authorization** and **clearance**, not "approval," as Section 17.5 explained. And they are for headaches, not for anxiety, IBS, or Crohn's disease.

One ear device does have an FDA decision for a gut condition, and it was made for teens. On June 7, 2019, the FDA granted a De Novo authorization to IB-Stim, a prescription-only stimulator worn behind the ear. Tiny needle electrodes deliver mild pulses to branches of several nerves around the ear, including a branch of the vagus nerve. It is authorized for patients 11 to 18 years old with abdominal pain from IBS, worn for up to 3 weeks, as an aid to reduce pain alongside other IBS treatments. The FDA based its decision mainly on about 50 teens with IBS inside one sham-controlled trial of 115 adolescents. The 2025 pediatric guideline from ESPGHAN and NASPGHAN suggests this kind of ear stimulation as a treatment option (a conditional recommendation, moderate-certainty evidence). So it is authorized, not approved; it is for IBS pain in teens, not for anxiety or Crohn's disease; and it is a prescription medical device, not a consumer gadget.

Consumer gadgets are a different category

Now Sam's ad. A **consumer wellness device** is a product sold directly to the public that claims to support general health or well-being, such as relaxation or stress relief, and is marketed without having to show the FDA that it treats any disease. The FDA has a "general wellness" policy for low-risk products that promote a healthy lifestyle; the latest version of the guidance page was updated in January 2026. These products aren't reviewed like medical devices, which is exactly why they shouldn't claim to treat a disease like an anxiety disorder.

Do these gadgets even affect the vagus nerve? Scientists often use heart rate variability (small beat-to-beat changes in heart rate, partly controlled by the vagus nerve) as a possible sign of vagus activity. A 2021 "living" meta-analysis by Wolf and colleagues pooled 16 studies in healthy people that compared ear-based stimulation with sham (fake) stimulation. It found strong evidence for **no effect** on this heart rate measure during stimulation. That doesn't rule out other effects, but this common heart-rate measure gave no sign that ear stimulation changes vagus activity, let alone that it cures anxiety.

Hype Meter: "This $300 vagus nerve gadget fixes anxiety"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. Consumer wellness gadgets are not the medical devices tested in clinical trials, and no vagus stimulator is FDA approved to treat anxiety. A 2021 meta-analysis of 16 sham-controlled studies in healthy people found ear stimulation did not change a common heart-rate sign of vagus activity. The approved, authorized, and cleared vagus-related devices are for epilepsy, treatment-resistant depression, rheumatoid arthritis, headaches, and (for one prescription ear stimulator) IBS pain in teens. **What would change the grade:** Large, sham-controlled trials of that specific device in people with diagnosed anxiety disorders, showing clear benefit, followed by an FDA decision for that use.

Ask "approved for what?"



Whenever someone says a vagus device is "FDA approved," ask two follow-up questions: approved, cleared, or authorized, and for which condition? The honest answer will usually be epilepsy, treatment-resistant depression, arm rehabilitation after stroke, rheumatoid arthritis, headache, or prescription-only teen IBS pain, not whatever the ad is selling.

17.9 Turning Down the Volume on Gut Pain: Tricyclic Antidepressants

Sam's IBS doesn't involve inflammation or tissue damage. As Chapter 10 explained, it's a disorder of gut-brain interaction: the gut and brain process signals in a way that turns ordinary sensations into pain and changes bowel habits. One treatment for this surprises many families.

A **tricyclic antidepressant** (TCA) is one of an older class of medicines, named for their three-ring chemical structure, that were first used for depression and are now also prescribed, usually in much lower doses, to reduce chronic pain, including gut pain in disorders of gut-brain interaction. When doctors use them this way, they act as gut-brain neuromodulators: medicines that change how pain signals are processed along the gut-brain axis.

Think of a stereo turned up so high that a quiet song blasts. A low-dose TCA is more like turning down the volume knob on pain signaling than changing the song.

What the evidence shows

- **Rome Foundation report (2018).** A team led by Drossman reviewed medicines for disorders of gut-brain interaction and concluded that low to modest doses of TCAs give the most convincing evidence of benefit for chronic gut pain. A related class, SNRIs, can also be recommended.
- **Network meta-analysis (2020).** Black and colleagues combined 51 randomized trials with 4,644 people with IBS. TCAs ranked second for overall IBS symptoms and first for abdominal pain. But the pain result

came from only 4 trials and 92 patients, only 13 of the 51 trials had a low risk of bias, and TCAs caused more side effects than placebo.

- **Guidelines.** The two main US guidelines agree that TCAs can help, but they rate the recommendation differently. The American College of Gastroenterology's 2021 IBS guideline makes a strong recommendation, based on moderate-quality evidence, that TCAs be used to treat overall IBS symptoms. The American Gastroenterological Association's 2022 guideline for IBS with diarrhea makes a conditional recommendation for TCAs, based on low-certainty evidence. "Conditional" means the experts think the benefits probably outweigh the risks for many patients, but the right choice depends more on the person.
- **The biggest trial (2023).** The ATLANTIS trial, described in the box below, tested low-dose amitriptyline in 463 people with IBS.
- **Children and teens (2025).** Almost all of this evidence comes from adults. The 2025 ESPGHAN/NASPGHAN pediatric guideline, for ages 4 to 18, says amitriptyline "may be suggested" for IBS and related belly pain, a conditional recommendation based on low-certainty evidence, and adds that it should only be prescribed by caregivers experienced in this area. Antidepressants, including amitriptyline, also carry an FDA warning: in studies, a small number of children, teens, and young adults up to age 24 had new suicidal thoughts or behavior while taking them. MedlinePlus notes that people under 18 normally should not take amitriptyline, though a doctor may decide it is the best choice for a particular young person. That is why, for teens, doctors weigh this option especially carefully and check in on mood.

Because amitriptyline's labeled use in the US is for depression (according to MedlinePlus, which lists other uses such as nerve pain and migraine prevention), prescribing a low dose for IBS is an example of **off-label use** backed by trials and guidelines.

"Does my doctor think it's all in my head?"

This is the question families ask most, and the answer is no. The doses used for gut pain are generally lower than those used for depression, and the goal is to calm pain signaling along the gut-brain axis. In the ATLANTIS trial, amitriptyline improved IBS symptoms, but an ACG summary of the trial reported no evidence that it changed depression scores. Most people in the trial weren't depressed to begin with, so the result fits the idea that the medicine works on gut symptoms rather than by treating depression, though the trial wasn't built to prove exactly how it works. Being offered a TCA for IBS means your doctor is treating a real problem in how your gut and brain communicate.

17.10 How to Read a Gut-Brain Claim: The ATLANTIS Trial

In 2023, Ford and colleagues in England published the ATLANTIS trial in *The Lancet*. They recruited adults with IBS (by Rome IV criteria) from 55 general medical practices whose symptoms continued despite first-line treatments such as diet changes. Participants were randomly assigned to a low dose of amitriptyline or a placebo for 6 months, and they could slowly adjust the dose within a set range based on symptoms and side effects. Nobody (participants, their doctors, or the researchers) knew who got which. The primary outcome was a standard IBS symptom severity score at 6 months.

At 6 months, the amitriptyline group's symptom scores were about 27 points better than the placebo group's, a statistically significant difference. The authors concluded that low-dose amitriptyline was superior to placebo and safe. An ACG evidence summary, written by an outside expert, called the trial "a major achievement" but noted that the average benefit was modest and did not reach the 35-point difference often considered meaningful to patients; more people in the amitriptyline group did report relief of their overall symptoms. About 13% stopped amitriptyline because of side effects, compared with 9% on placebo.

How to read a gut-brain claim: the 2023 ATLANTIS trial

Question	This study
Mouse or human?	Human: 463 adults with IBS in primary care in England.
Correlation or cause?	Tests cause: randomized, double-blind, placebo-controlled, with a primary outcome set in advance.
How many?	463 people (232 amitriptyline, 231 placebo), the largest trial of a TCA in IBS so far, according to its authors.
How long?	6 months of treatment, longer than most earlier IBS drug trials (often 4 to 12 weeks).
Who paid for it?	The UK National Institute for Health and Care Research, a government research funder.
Is something being sold?	No company product is being promoted. Amitriptyline is an old, inexpensive generic medicine.

The conclusion: this is strong evidence that low-dose amitriptyline helps IBS symptoms more than placebo, in adults, over 6 months. The average size of the benefit was modest, it caused side effects for some people, and the trial didn't include teens. It does not mean every person with IBS should take a TCA. That's a benefit-risk decision for each patient and doctor.

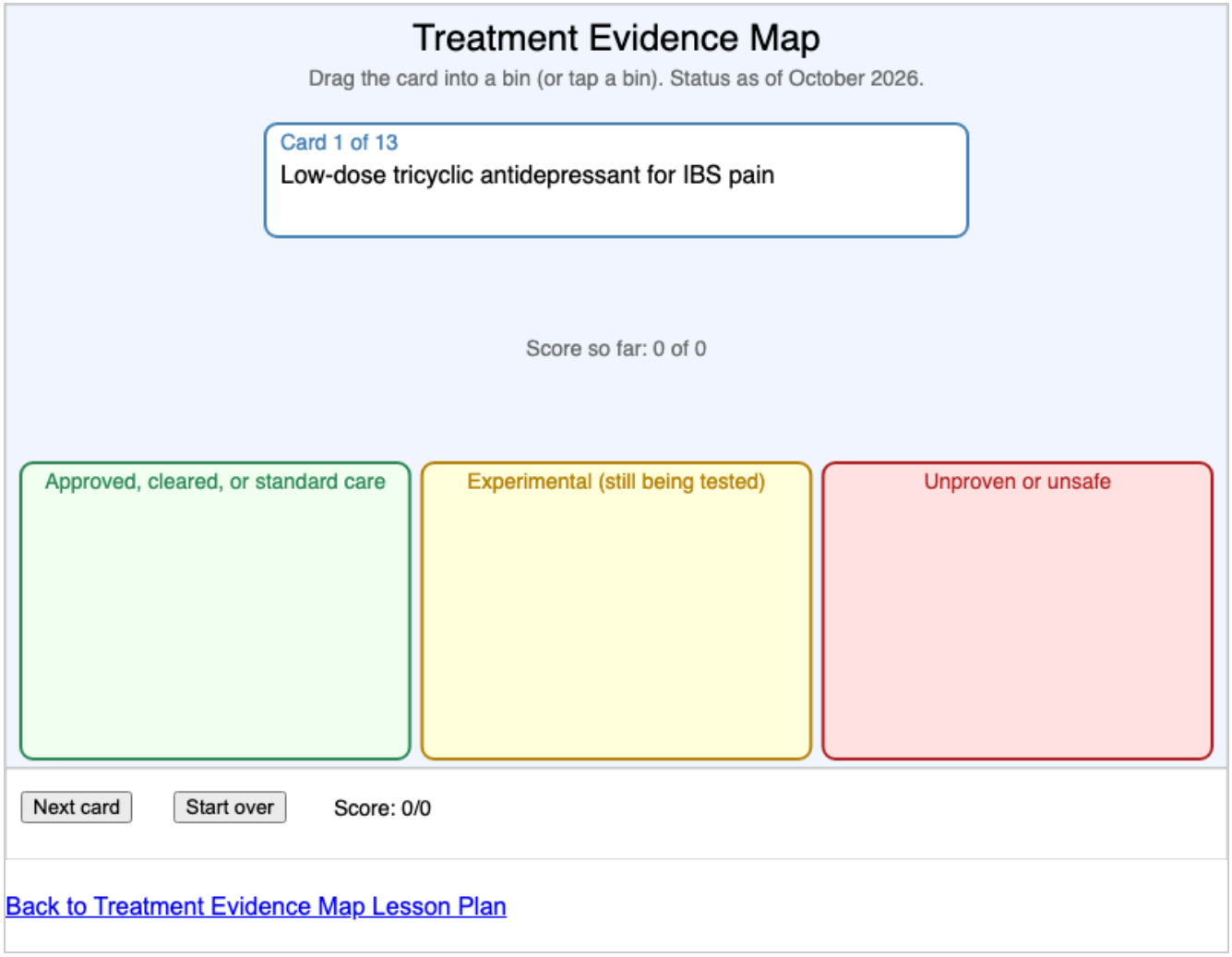
If you're going through this

If your doctor suggests a medicine called an "antidepressant" for gut pain, it's okay to feel surprised, or even a little insulted. Ask what dose they mean, how it's supposed to help your gut, what side effects to watch for (including changes in mood, which matter for anyone under 25), and how long before you'd know if it's working. You can also ask about other options, like gut-directed therapy, which Chapter 18 covers. Your symptoms are real, and choosing a treatment is a decision you get to make together with your care team.

17.11 Try It Yourself: The Treatment Evidence Map

Time to sort what you've learned. In the simulation below, treatment cards appear one at a time. Drag each card (or tap a bin) to sort it into **Approved, cleared, or standard care**; **Experimental (still being tested)**; or **Unproven or unsafe**. After each choice, a panel explains the right answer with the evidence from this chapter.

Diagram: Treatment Evidence Map



Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch17-treatment-evidence-map/main.html

Open the Treatment Evidence Map fullscreen

MicroSim specification: Treatment Evidence Map

Type: microsim **sim-id:** ch17-treatment-evidence-map
Library: p5.js
Status: Implemented
Bloom Level: Evaluate
Bloom Verb: classify, judge
Learning Objective: The learner will classify gut-brain treatments by FDA status and strength of evidence (approved, cleared, or standard care; experimental; unproven or unsafe) and justify each choice with evidence.

Canvas: 500 px drawing area plus 60 px controls (iframe 562 px); responsive to about 380 px wide.

Controls: Drag the card, or tap a bin, to sort it; Next card button; Start over button (reshuffles).

Cards (13): microbiome product for recurrent C. diff; FMT for ulcerative colitis; FMT for autism; DIY FMT; implanted VNS for epilepsy; implanted VNS for treatment-resistant depression; implanted VNS for rheumatoid arthritis; VNS for Crohn's disease; gammaCore for cluster headache; consumer ear-clip gadget for anxiety; low-dose TCA for IBS; biologic for Crohn's disease; FMT for Parkinson's disease.

Feedback: Immediate correct or not-quite message with a one-sentence evidence reason; sorted cards appear in each bin with check or cross marks; running score.

Provenance: Sections 17.3 to 17.9; statuses as of October 2026.

Try to sort all 13 cards before looking back at the chapter. Pay special attention to the vagus nerve cards: the same basic technology lands in different bins depending on the condition, because approval is always for a specific use. When you get one wrong, ask which word on the card you missed: the condition, the type of device, or the kind of evidence.

What this model leaves out

- Real evidence comes in shades, not three bins. "Experimental" covers everything from a 7-person pilot study to large trials that are almost finished.
- Approval status changes over time, and statuses differ between countries. The sim reflects the US as of October 2026.
- "Approved" or "standard care" doesn't mean right for every person; the benefit-risk balance depends on the individual.
- The sim doesn't show cost, insurance, access, or side effects, all of which matter in real decisions.
- Card reasons are one-sentence summaries; the chapter and its sources have the full details.

17.12 Making the Choice Together

Knowing what's approved is only the start. Most treatment decisions have more than one reasonable option, and the right one depends on things only the patient can judge, like how much a side effect would bother them or how they feel about surgery.

Shared decision-making is a process in which a patient (and, for a teen, often their family) and their clinician decide on a treatment together, combining the clinician's knowledge of the evidence with the patient's own values, goals, and preferences. The doctor explains the options, including waiting, with their likely benefits and risks, and the patient explains what matters to them.

Good questions to bring to these conversations include:

1. What are my options, including not treating it right now?
2. What are the likely benefits and the possible harms of each?
3. How strong is the evidence, and was it tested in people like me (my age, my condition)?
4. Is this use approved, off-label, or experimental?
5. What happens next if it doesn't work?

Medicine is also trying to get better at matching treatments to individuals from the start. **Precision medicine**, as defined by the US Precision Medicine Initiative and explained by MedlinePlus, is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." It contrasts with a one-size-fits-all approach. In gut-brain medicine, researchers hope a person's microbiome, genes, or nerve signals could someday predict who will respond to FMT, a probiotic strain, or a stimulator. That's research, not routine care today, but the mixed results in this chapter are part of why scientists want it.

For families

When your teen faces a treatment decision, the most helpful thing you can do is help them ask questions, not answer for them. Bring the list of five questions above to appointments, and let your teen speak first. If a relative pushes a treatment they saw online, like a home "fecal transplant" or a vagus gadget, you can say, "We're going to check that with the care team," which respects the relative and protects your child. And if your teen is offered a low-dose antidepressant for gut pain, avoid saying "So it's all in your head?" The medicine is treating real pain signaling.

At the Bedside: When the Infection Keeps Coming Back

Meet the patient (fictional)

Helen is 71 and lives on her own. After a course of antibiotics for pneumonia last winter, she developed severe watery diarrhea and was diagnosed with *C. difficile* infection. Antibiotics cleared it, but it came back two months later, and then again. She has now had three episodes. She's lost weight, is afraid to leave the house in case she can't reach a bathroom, and has stopped going to her book club. Her daughter, who lives an hour away, has started calling every day.

What the doctor checks: Her gastroenterologist reviews the timeline of her infections and treatments, checks for dehydration and kidney function, confirms the current episode with stool testing for *C. difficile*, and reviews her other medicines and her immune status. The doctor also asks how the infections are affecting her daily life and mood.

Connecting the signals: Each round of antibiotics kills *C. diff* but also keeps her normal gut bacteria from recovering, so the "bare lawn" invites the infection back. Her age raises her risk too. Her doctor explains that what she needs isn't just another antibiotic, but a way to restore the microbial community that normally keeps *C. diff* in check.

Diagnosis: Recurrent *C. difficile* infection (second recurrence, her third episode).

Why it happens: As Section 17.2 explained, antibiotics disrupt the gut microbiome and give *C. diff* room to grow, and the risk of another recurrence rises with each episode. Microbiome-based treatments work by replanting the missing community.

The mind-body side: Months of unpredictable diarrhea have left Helen anxious, isolated, and embarrassed. Her care team takes that seriously. They talk with her about what to expect, connect her with a social worker, and encourage her daughter to help with practical support rather than worried daily calls. Her doctor is careful with expectations: the treatment has a very good track record, but it is not a guarantee, and a small number of people still have another recurrence.

Treatment today: After antibiotic treatment for the current episode, her doctor discusses her options using shared decision-making: one of the two FDA-approved microbiome products (Rebyota, given once rectally, or Vowst, capsules taken over three days), both approved to prevent recurrence in adults after antibiotic treatment for recurrent infection, or FMT from a screened donor through her hospital's program. They go through the benefits, the small risk of transmitting infections from donor material, and what she'd prefer. Helen chooses the capsules because she'd rather avoid another procedure.

What's new in research: The 2023 Cochrane review concluded that, in adults with healthy immune systems, FMT likely leads to a large increase in resolution of recurrent *C. diff*, with about 3 people treated for one additional cure. It also said more data, such as from large national registries, are needed to understand longer-term risks, and that too few people with weakened immune systems have been studied to draw conclusions for them. **Evidence grade: Strong** for preventing recurrent *C. diff* in adults with healthy immune systems; long-term safety is still being studied.

Your turn: reason through a variation

Helen's friend Rosa, who is 68, has ulcerative colitis. She hears about Helen's recovery and asks her own doctor whether she can take the same capsules for her colitis. What should her doctor explain?

Answer: Vowst and Rebyota are FDA approved only to prevent recurrent *C. diff* infection in adults after antibiotics, not for ulcerative colitis. A 2023 Cochrane review found that FMT may help some people with active ulcerative colitis reach remission, but the evidence is low certainty, so it remains experimental. Using an approved product for a different disease would be off-label without good evidence, and the benefit-risk balance is unknown. Her doctor might mention clinical trials she could ask about, alongside her proven colitis treatments.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: If a treatment is "natural," like a stool transplant, it must be safe.
Reality: Stool can carry dangerous germs. In 2019, a drug-resistant *E. coli* infection traced to one FMT donor killed a patient, even with screening. FMT is powerful medicine with real risks, which is why it's done with screened donors and tested stool.

Myth: Doing your own fecal transplant at home is basically the same as getting one at a hospital.
Reality: Medical FMT depends on donor screening, stool testing, and follow-up. Homemade versions skip all of them, so the risk of passing on an infection is much higher, and they're done for conditions where FMT hasn't been proven to help.

Myth: If a treatment is FDA approved for one condition, it's approved for related conditions too.
Reality: FDA approval is always for a specific use. Vagus nerve stimulators are approved for epilepsy,

treatment-resistant depression, arm-movement rehabilitation after stroke (the Vivistim System), and rheumatoid arthritis, but not for Crohn's disease, IBS, or anxiety (a separate ear device, IB-Stim, is authorized only for IBS belly pain in patients 11 to 18), and Vowst and Rebyota are approved only to prevent recurrent *C. diff*.

Myth: If your doctor prescribes an antidepressant for IBS, they think your symptoms are all in your head.
Reality: Low-dose tricyclic antidepressants are used to calm pain signaling along the gut-brain axis. In the 2023 ATLANTIS trial, amitriptyline improved IBS symptoms without evidence of changing depression scores. It treats a real problem in gut-brain communication.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "FDA-approved vagus nerve stimulation is now available to heal your gut and calm your anxiety. Order our clinic-grade ear device today!"

Grade: Hype. The FDA-approved implanted VNS devices are for drug-resistant epilepsy, treatment-resistant depression in adults, arm-movement rehabilitation after stroke, and rheumatoid arthritis, and the handheld gammaCore is authorized and cleared for cluster headache and migraine. None is approved for gut disorders or anxiety; the closest is a prescription ear stimulator (IB-Stim) that is authorized only as an add-on for IBS pain in 11- to 18-year-olds, which is not what this ad is selling. A consumer ear gadget is a different product from the devices tested in trials, and a 2021 meta-analysis found ear stimulation didn't change a common heart-rate sign of vagus activity in healthy people. A careful version would say: "Vagus nerve stimulation is FDA approved for a few specific conditions; its use for gut disorders and anxiety is still being researched."

2. Predict: Riya reads that her friend's grandfather had FMT and his recurrent C. diff never came back. She wonders whether FMT would work as well for her Crohn's disease. What would you predict, based on the evidence?

FMT probably would not work as reliably for Crohn's as it does for recurrent *C. diff*, and nobody knows for sure. *C. diff* is a single germ taking over a disrupted microbiome, so replanting the community directly fixes the problem. Crohn's disease involves the immune system, genes, and the environment, and a 2023 Cochrane review found the evidence for FMT in Crohn's very uncertain. Riya's biologic has much stronger evidence, so this is a question for Dr. Alvarez and possibly a future clinical trial.

3. Explain: Why is the SetPoint System approved for rheumatoid arthritis, a disease of the immune system, even though it stimulates a nerve?

It's based on the inflammatory reflex: the brain senses inflammation and sends signals back through the vagus nerve that calm the release of inflammatory chemicals like cytokines. Stimulating the left vagus nerve is meant to switch on that calming signal. In the RESET-RA trial summarized by the FDA, 35.2% of people with active stimulation versus 24.2% with sham stimulation improved by at least 20% on an arthritis scale after 12 weeks. The approval is only for adults with moderate to severe rheumatoid arthritis whose biologic or targeted drugs didn't work well.

4. Apply: Sam's doctor suggests a low-dose tricyclic antidepressant for his IBS pain, and Sam's cousin Dev says, "See? They think you're crazy." How could Sam respond using this chapter?

Sam could explain that low doses of TCAs are used as gut-brain neuromodulators to turn down pain signaling, and that US guidelines support them for IBS (a strong recommendation from the ACG and a conditional one from the AGA). In the large ATLANTIS trial, amitriptyline improved IBS symptoms without evidence of changing depression scores. Using it for IBS is off-label but backed by trials. Sam can also tell Dev that whether to try it is a decision he'll make with his doctor, weighing the possible side effects. Because Sam is 16, his doctor will be extra careful: the 2025 pediatric guideline gives amitriptyline only a conditional recommendation, and antidepressants carry a warning about mood changes in young people.

5. Read the data. In the 2013 van Nood trial, adults with recurrent *C. diff* were randomly assigned to three treatments. Here's the share whose infection resolved without relapse at 10 weeks:

Treatment group	Cured	Total	Percent
Donor stool infusion (first infusion)	13	16	81%
Vancomycin alone	4	13	31%
Vancomycin plus bowel cleanse	3	13	23%

5. What does this data show, and what can't it show?

It shows a large difference: about 81% cured with donor stool versus about 23 to 31% with antibiotics alone, in a randomized trial, so the difference is likely caused by the treatment. Including a bowel-cleanse group shows the cleanse alone wasn't responsible. But the trial was small (42 people), was stopped early, and included only adults with recurrent infection, so it can't tell us about first infections, children, people with weak immune systems, or long-term safety. The 2023 Cochrane review, pooling 6 trials with 320 people, helps by confirming the benefit across more studies.

Exercises

Remember

1. What two FDA-approved products are made from donated human stool, when was each approved, and what are they approved for?

Answer

Rebyota (approved November 30, 2022, given rectally) and Vowst (approved April 26, 2023, oral capsules). Both are approved to prevent *C. diff* infection from coming back in adults 18 and older after antibiotic treatment for recurrent infection.

1. List the four conditions for which implanted vagus nerve stimulators are FDA approved, with the year of each approval.

Answer

Drug-resistant partial-onset epilepsy as an add-on (1997); chronic or recurrent treatment-resistant depression in adults as an add-on after 4 or more failed treatments (2005); arm-movement rehabilitation after a chronic ischemic stroke (Vivistim System, August 27, 2021); and moderate to severe rheumatoid arthritis in adults who didn't respond to biologic or targeted drugs (SetPoint System, July 30, 2025).

Understand

1. Explain the difference between FDA "approval," "clearance," and "authorization" for a medical device, using gammaCore and implanted VNS as examples.

Answer

Approval (premarket approval) is the FDA's most stringent device review, requiring scientific evidence of safety and effectiveness, used for high-risk devices like implanted VNS. A De Novo authorization is for a new type of lower-risk device with no existing equivalent, as with gammaCore for cluster headache in 2017. A 510(k) clearance means a device is substantially equivalent to one already on the market, as with gammaCore's migraine use in 2018.

1. Explain why antibiotics can lead to *C. diff* infection, and why FMT helps.

Answer

Antibiotics kill many normal gut bacteria that usually keep *C. diff* from growing, so *C. diff* can take over and cause infection. More antibiotics kill *C. diff* but keep the normal community from recovering, so it often comes back. FMT replants a healthy donor's microbial community, which can crowd out *C. diff* and prevent recurrence.

Apply

1. A news headline says, "Nerve zapper approved by FDA could treat Crohn's disease." Using Section 17.7, identify what is accurate and what is misleading, and rewrite the headline accurately.
2. Use the Treatment Evidence Map to sort all 13 cards. Record your score, list any cards you got wrong, and for each, explain which detail (condition, type of device, or type of evidence) you missed.

Analyze

1. Compare the evidence for FMT in recurrent *C. diff*, ulcerative colitis, and autism. For each, describe the type of study, its size, and whether it had a control group. Explain why the same procedure earns such different grades.
2. The SetPoint System's pilot study (14 patients, company-funded) and its RESET-RA trial (242 patients, sham-controlled) both supported approval. Analyze what each study adds and what questions remain, including why the trial's 12-month results, measured after the sham group ended, are harder to interpret than its 12-week results.

Evaluate

1. A parent argues: "If doctors can prescribe drugs off-label, why can't I give my child an unapproved supplement?" Evaluate this argument using the ideas of off-label use, benefit-risk balance, and the regulation differences from Chapters 16 and 17.
2. Judge whether low-dose tricyclic antidepressants for IBS deserve the label "standard care." Use the Black 2020 meta-analysis, the guideline recommendations, and the ATLANTIS trial, and include at least one limitation.

Create

1. Design a Phase 2 clinical trial testing whether vagus nerve stimulation helps adults with Crohn's disease. Describe your participants, groups (including a sham), blinding, length, primary outcome, safety monitoring, and what result would justify moving to Phase 3.

2. Create a one-page "question card" a teen could bring to an appointment when discussing a new gut-brain treatment. Use the ideas of FDA approval, off-label use, benefit-risk balance, and shared decision-making, written in plain language.

Key Takeaways

- *C. difficile* infection often follows antibiotics and frequently comes back. Fecal microbiota transplant from screened donors clears recurrent infection far better than antibiotics alone (about 3 people treated per extra cure), but DIY FMT is unsafe.
- Rebyota (November 30, 2022) and Vowst (April 26, 2023) are FDA-approved live biotherapeutic products made from donated stool, approved only to prevent recurrent *C. diff* in adults after antibiotics. FMT for ulcerative colitis, Crohn's, autism, and Parkinson's remains experimental.
- FDA approval is always for a specific use. Devices can be approved (PMA), authorized (De Novo), or cleared (510(k)), and doctors may prescribe approved drugs off-label when medically appropriate.
- Implanted vagus nerve stimulators are FDA approved for drug-resistant epilepsy (1997), treatment-resistant depression in adults (2005), arm-movement rehabilitation after stroke (Vivistim System, 2021), and rheumatoid arthritis (July 30, 2025), building on the inflammatory reflex and the field of bioelectronic medicine. They are not approved for Crohn's, IBS, or anxiety.
- The noninvasive gammaCore is authorized and cleared for cluster headache (2017) and migraine (2018). Consumer "vagus" wellness gadgets are not the devices tested in trials, and claims that they fix anxiety are Hype.
- Low-dose tricyclic antidepressants calm gut pain signaling in IBS; they're off-label but supported by trials (mostly in adults) and guidelines, they need extra care in young people, and they don't mean symptoms are "in your head."
- Every treatment choice is a benefit-risk balance best made through shared decision-making, and precision medicine aims to match treatments to individuals in the future.

You can sort medicine from marketing!



You now know what's truly approved in gut-brain medicine, for exactly what, and how to ask the right questions about everything else. Next, in Chapter 18, we'll look at treatments you don't get from a pharmacy at all: sleep, exercise, and gut-directed therapy.

Quiz: Medicine for the Gut-Brain Axis

Test your understanding of Chapter 17. Choose the best answer, then click **Show Answer** to check.

Question 1

What are Rebyota and Vowst FDA approved for?

A. Treating ulcerative colitis and Crohn's disease in teens and adults

B. Treating a first episode of C. difficile infection in children

C. Preventing C. difficile infection from coming back in adults 18 and older, after antibiotic treatment for recurrent infection

D. Restoring a healthy microbiome in anyone who has taken antibiotics

Show Answer

The correct answer is **C**. Rebyota (November 30, 2022) and Vowst (April 26, 2023) are approved only to prevent recurrence of *C. difficile* infection in adults after antibiotic treatment for recurrent infection. Option A is a common mix-up: FMT for IBD is still experimental, and neither product is approved for it.

Concept Tested: Live Biotherapeutic Product **Bloom's Level:** Remember

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Question 2

In what year was an implanted vagus nerve stimulator first FDA approved, and for what condition?

A. 1997, as an add-on treatment for drug-resistant partial-onset epilepsy

B. 2005, for all adults with depression

C. 2017, for cluster headache

D. 2025, for Crohn's disease

Show Answer

The correct answer is **A**. The VNS Therapy System was first approved on July 16, 1997, as an add-on treatment for drug-resistant partial-onset seizures. The 2005 approval (option B) was only for adults with treatment-resistant depression, and the 2025 approval was for rheumatoid arthritis, not Crohn's disease.

Concept Tested: Implanted VNS Device **Bloom's Level:** Remember

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Question 3

According to the FDA, what is the main purpose of a Phase 1 clinical trial?

A. Confirming that a drug works in thousands of patients

B. Monitoring safety after the drug is approved

C. Comparing the drug against all other treatments on the market

D. Testing safety and dosage in a small group of people

Show Answer

The correct answer is **D**. The FDA describes Phase 1 as testing safety and dosage in about 20 to 100 healthy volunteers or people with the condition. Option A describes Phase 3, and option B describes Phase 4, which happens after approval.

Concept Tested: Clinical Trial Phases **Bloom's Level:** Remember

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Question 4

The gammaCore handheld device received a De Novo authorization in 2017 and a 510(k) clearance in 2018. Why is it inaccurate to say gammaCore is "FDA approved"?

A. Because the FDA has never reviewed it

B. Because authorization and clearance are different FDA device pathways from premarket approval, which is the most stringent review

C. Because it is only available outside the United States

D. Because it is a dietary supplement, not a device

Show Answer

The correct answer is **B**. The FDA did review gammaCore, but through the De Novo (authorization) and 510(k) (clearance) pathways, not premarket approval, which the FDA calls its most stringent device review. Option A is wrong because authorization and clearance are real FDA decisions.

Concept Tested: Noninvasive VNS **Bloom's Level:** Understand

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Question 5

How is the inflammatory reflex thought to work?

A. Gut bacteria release electricity that travels to the brain.

B. The immune system sends antibodies along the vagus nerve to the brain.

C. The nervous system senses inflammation and sends signals, largely through the vagus nerve, that calm the release of inflammatory chemicals.

D. Inflammation in the gut automatically switches off the brain's pain centers.

Show Answer

The correct answer is **C**. Kevin Tracey described the inflammatory reflex in 2002: nerve circuits regulate inflammation in real time, and cholinergic (acetylcholine-using) neurons can shut down acute inflammation. Option B confuses nerve signals with immune molecules; nerves carry electrical and chemical signals, not antibodies.

Concept Tested: Inflammatory Reflex **Bloom's Level:** Understand

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Question 6

Why do doctors prescribe low-dose tricyclic antidepressants for some people with IBS?

A. Because IBS is a form of depression

B. Because the medicines kill harmful gut bacteria

C. Because they are FDA approved specifically for IBS

D. Because, at low doses, they act as gut-brain neuromodulators that calm pain signaling

Show Answer

The correct answer is **D**. Low-dose TCAs are used to turn down pain signaling along the gut-brain axis, and in the ATLANTIS trial amitriptyline improved IBS symptoms without evidence of changing depression scores. Option C is wrong: using them for IBS is off-label, though supported by trials and US guideline recommendations.

Concept Tested: Tricyclic Antidepressant **Bloom's Level:** Understand

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Question 7

Marcus, 15, sees an ad: "Our ear-clip vagus stimulator is backed by the same science as FDA-approved devices. Say goodbye to anxiety!" Which response best fits the evidence?

A. Be skeptical: consumer wellness gadgets aren't the devices tested in trials, and no vagus stimulator is approved to treat anxiety.

B. Trust it, because implanted VNS is FDA approved, so all vagus devices work.

C. Trust it, because the ad says "science."

D. Avoid all vagus nerve treatments, since none are ever approved.

Show Answer

The correct answer is **A**. Approval is always for a specific device and use; implanted VNS is approved for epilepsy, treatment-resistant depression, arm-movement rehabilitation after stroke (the Vivistim System), and rheumatoid arthritis, not anxiety. A 2021 meta-analysis also found ear stimulation didn't change a heart-rate sign of vagus activity in healthy people. Option D overcorrects, since several VNS devices are approved or cleared for specific conditions.

Concept Tested: Consumer Wellness Device **Bloom's Level:** Apply

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Question 8

A doctor prescribes an approved medicine for a condition not listed on its official label, because no approved drug works well for that condition. What is this called, and what does the FDA say about it?

A. Illegal prescribing, which the FDA does not allow

B. Off-label use, which providers may choose when medically appropriate, though FDA hasn't determined the drug is safe and effective for that use

C. Expanded approval, which automatically adds the condition to the label

D. A Phase 4 trial, which the FDA requires for every prescription

Show Answer

The correct answer is **B**. The FDA explains that once a drug is approved, providers generally may prescribe it for an unapproved use when they judge it medically appropriate, but the FDA has not determined it is safe and effective for that use. Option A is a common misunderstanding; off-label prescribing is legal.

Concept Tested: Off-Label Use **Bloom's Level:** Apply

Question 9

In the 2013 van Nood trial, 81% of patients given donor stool were cured of recurrent C. diff, compared with 31% on vancomycin alone. Which conclusion is best supported?

A. FMT works for every gut disease linked to the microbiome.

B. FMT is completely safe because no deaths occurred in this trial.

C. The trial proves FMT works in children and people with weak immune systems.

D. In adults with recurrent C. diff, FMT likely caused much higher cure rates, though the trial was small and stopped early.

Show Answer

The correct answer is **D**. Random assignment means the large difference was likely caused by the treatment, but the trial had only 42 people and studied adults with recurrent infection. Option B is wrong: a small trial can't rule out rare harms, and a 2019 report linked one FMT donor to a fatal drug-resistant infection.

Concept Tested: Fecal Microbiota Transplant **Bloom's Level:** Analyze

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Question 10

Why does FMT have a strong benefit-risk balance for an adult with a third C. diff recurrence, but a poor one for a healthy person who wants to "optimize" their gut?

A. Because FMT only has risks in healthy people

B. Because healthy people have no gut bacteria to replace

C. Because the benefit is large and proven for recurrent C. diff, while there is no proven benefit for the healthy person, so any risk outweighs it

D. Because the FDA bans FMT for anyone without C. diff

Show Answer

The correct answer is **C**. Benefit-risk balance weighs how much a treatment is likely to help against its possible harms for a specific person. For recurrent *C. diff*, about 3 people need to be treated for one extra cure, so a small infection risk is worth it; with no proven benefit, the same risk isn't. Option A is wrong because the infection risk exists for everyone who receives donor material.

Concept Tested: Benefit-Risk Balance **Bloom's Level:** Analyze

Chapter 18: Sleep, Exercise, and Therapy

Summary

The gut-brain axis does not switch off when you fall asleep, lace up your running shoes, or sit down with a therapist. This chapter explains how your body's internal clock and the stages of sleep connect to inflammation, gut microbes, and gut symptoms, and why teens need more sleep than most of them get. It then looks at what exercise really does for gut movement and mood, and at the best-studied brain-gut psychotherapies for IBS, including cognitive behavioral therapy and gut-directed hypnotherapy, plus mindfulness and slow breathing. Finally, it teaches you to keep a symptom diary like a scientist: noticing patterns without jumping to conclusions that a week of data can't support.

Concepts Covered

1. Circadian Rhythm
2. Sleep Architecture
3. Teen Sleep Need
4. Sleep and Inflammation
5. Microbiome Daily Rhythm
6. Sleep Hygiene
7. Physical Activity
8. Exercise and Gut Transit
9. Exercise and Mood
10. Psychotherapy
11. Brain-Gut Psychotherapy
12. Mindfulness
13. Slow Breathing
14. Heart Rate Variability
15. Self-Monitoring
16. Behavior Change

Prerequisites

- Chapter 2: The Vagus Highway (the parasympathetic "rest and digest" pathway)
- Chapter 4: The Immune System as a Sense Organ (cytokines and how inflammation affects the brain)
- Chapter 7: Stress and the Gut (the HPA axis and cortisol)
- Chapter 8: Pain, Sensitivity, and the Gut (visceral hypersensitivity)
- Chapter 10: IBS and Disorders of Gut-Brain Interaction (what IBS is and how it is diagnosed)

Everyday levers on the gut-brain axis



Most of this book has been about signals you can't see or steer directly. This chapter is about things you do every day: sleeping, moving, breathing, and how you talk to yourself about symptoms. These are real levers on the gut-brain axis, but they're also magnets for hype, so we'll check the evidence for each one. And because I run right past the heart on my way down, I get a starring role in the section on breathing.

18.1 Sam's Bad Nights and Bad Gut Days

Sam has started keeping notes on his phone. He runs cross-country, he has IBS with mixed bowel habits, and he has noticed something: his worst gut days seem to come after his worst nights. The Wednesday before his chemistry test, he slept about five hours, woke up with cramps, and spent first period worrying about where the nearest restroom was. The Saturday after a race, he slept nine hours and felt fine. (Sam is a fictional student who appears throughout this book.)

So is it the sleep? Sam's first thought is yes. But his friend Riya, who has Crohn's disease, points out a problem. "The night before the test, you were also stressed. And you stayed up late. And you probably ate dinner at 11. How do you know which one did it?" Sam doesn't. That question runs through this whole chapter, because sleep, exercise, stress, and therapy all touch the gut-brain axis and all tangle together in real life.

Riya has her own version. Before the orchestra's winter concert, she practiced violin past midnight almost every night. Her Crohn's is mostly in remission, but she wonders whether those short nights matter for her gut. This chapter looks at what the research says about both questions, and gives you a tool for asking them carefully.

18.2 Your Body Runs on Clocks

Think of a school bell schedule. Even if you never look at a clock, the bells tell everyone when to move, when to eat lunch, and when the day is over. Your body has its own bell schedule, and it rings for far more than sleep.

A **circadian rhythm** is a roughly 24-hour cycle in the body's functions, such as sleepiness, body temperature, hormone release, and digestion, that is driven by an internal clock and kept in step with the outside world, mostly by light. ("Circadian" comes from Latin words meaning "about a day.") According to the National

Institute of Neurological Disorders and Stroke (NINDS), these rhythms are why you tend to feel sleepy at night and can wake without an alarm.

The master clock sits deep in the brain. NINDS describes the suprachiasmatic nucleus (SCN) as a cluster of thousands of cells in the hypothalamus that receives information about light directly from the eyes. The SCN signals the pineal gland, which releases the hormone melatonin as it gets dark, helping you feel ready to sleep. For a refresher on brain states and the sleep circuits of the brainstem and hypothalamus, see From Neuron to Bedside, Chapter 10.

Your gut keeps time too. As you'll see in Section 18.5, even the microbes living in your gut rise and fall on a daily schedule, and that schedule is set largely by when you eat. So the body really has two kinds of timing cues: light, which sets the brain's master clock, and meals, which help set the rhythm inside the gut. When the two get out of step, it's a bit like two marching bands playing the same song half a beat apart.

Why teens can't just "go to bed earlier"

Biology makes "just go to bed earlier" harder than it sounds. In 2014, the American Academy of Pediatrics (AAP) published a policy statement on school start times. It explains that around puberty, the timing of sleep shifts later, by up to 2 hours compared with middle childhood, partly because melatonin is released later at night across adolescence. Many teens simply aren't sleepy at 9:30 p.m., even when they're exhausted.

The AAP called school start times before 8:30 a.m. a key, changeable cause of teen sleep loss and recommended that middle and high schools start no earlier than 8:30 a.m. When Riya can't fall asleep after a late practice, part of the problem is her schedule and part is a teen body clock running later than the school bell.

18.3 Inside a Night of Sleep

Sleep is not one long blank. It's more like a playlist that repeats through the night, with different tracks doing different jobs.

Sleep architecture is the structure of a night's sleep: the pattern of stages (light non-REM sleep, deep non-REM sleep, and REM sleep) and how they cycle and change across the night. NINDS describes it this way:

Stage	What happens	When it shows up
Non-REM stage 1	The changeover from waking to sleep. Heartbeat, breathing, and eye movements slow; brain waves begin to slow.	Lasts several minutes at the start of a cycle
Non-REM stage 2	Light sleep. Heart rate and breathing slow further and body temperature drops.	The stage you spend the most time in overall

Stage	What happens	When it shows up
Non-REM stage 3	Deep sleep, the kind you need to feel refreshed. Heartbeat and breathing reach their lowest levels; it is hard to wake someone up.	Longer periods in the first half of the night
REM sleep	Eyes move rapidly; brain activity looks closer to waking; most dreaming happens. Breathing, heart rate, and blood pressure rise toward waking levels.	First appears about 90 minutes after falling asleep; REM periods get longer later in the night

You cycle through non-REM and REM several times a night. Because deep sleep is concentrated early and long REM periods come late, cutting a night short from either end removes different kinds of sleep. Riya's late practices cut the beginning of her night, and her 6:30 a.m. alarm cuts the end.

How much sleep teens need

Teen sleep need is the amount of sleep recommended for adolescents to support health, learning, and mood. In 2016, the American Academy of Sleep Medicine (AASM) published a consensus statement (Paruthi and colleagues) recommending that teenagers 13 to 18 years old sleep 8 to 10 hours per 24 hours on a regular basis. The Centers for Disease Control and Prevention (CDC) lists the same 8 to 10 hours for ages 13 to 17.

Most teens fall short. In the CDC's 2025 Youth Risk Behavior Survey, only 24% of US high school students said they got at least 8 hours of sleep on an average school night, about 1 in 4. Sam and Riya are in the majority.

Short sleep is the normal teen experience, not a personal failure



When three out of four high school students don't hit 8 hours, the cause isn't three out of four people being lazy. Body clocks, early bells, homework, practices, and phones all push in the same direction, so fixing sleep is partly a personal project and partly a school and family one.

18.4 Sleep, Inflammation, and the Gut

Why would a short night touch the gut at all? One route goes through the immune system, which you met in Chapter 4.

Think of inflammation as the body's alarm-and-repair crew. **Sleep and inflammation** refers to the two-way link between sleep and the immune system: disturbed sleep is associated with higher levels of inflammatory signaling molecules in the blood, and inflammation (for example, during an infection or a disease flare) can in turn change sleep.

What does the human evidence show? In 2016, Irwin and colleagues pooled 72 studies with more than 50,000 adults. People with disturbed sleep (trouble falling or staying asleep, or poor-quality sleep) had slightly higher blood levels of two inflammatory markers, C-reactive protein (CRP) and interleukin-6 (IL-6). The effects were small. Surprisingly, very long sleep was also linked to higher CRP and IL-6, while the shortest sleep was not, and lab experiments that kept people awake did not reliably raise these markers. So the link is real but modest, and it is mostly correlation.

Sleep and Crohn's disease

Riya's question has a direct study behind it. In 2013, Ananthakrishnan and colleagues followed 3,173 adults with inflammatory bowel disease through an online research network. Among 1,291 people with Crohn's disease who were in remission at the start, those who reported poor sleep had about twice the odds of having active disease six months later, even after the researchers adjusted for other factors. The same link did not show up in people with ulcerative colitis.

This is an important finding, but read it carefully. It's an association. Poor sleep might nudge inflammation upward, or early, not-yet-noticed inflammation might already be disturbing sleep, or a third factor (like stress or pain) might affect both. The study can't separate these.

Sleep and IBS

For IBS, the clearest study is small. In 2014, Buchanan and colleagues asked 24 women with IBS to record their sleep and symptoms each day. After a night of poor sleep, the women reported more abdominal pain, more anxiety, and more fatigue the next day. But poor sleep did not predict next-day bowel symptoms or depressed mood, and daytime symptoms mostly did not predict the next night's sleep. With only 24 people, all women, this is a hint worth testing, not a rule.

For families

If your teen has a gut condition and is up late, try to treat sleep as part of their health plan rather than a discipline issue. Teen body clocks run later, so a lecture at 11 p.m. rarely helps; a family agreement about screens charging outside the bedroom, a steady wake-up time on weekends, and protecting sleep the week of a big event usually helps more. If sleep stays poor, or pain or bathroom trips are waking your teen up, tell the care team, because night-time symptoms are useful medical information.

18.5 Gut Microbes Keep Time Too

Your gut microbes are like a city whose streets look different at 8 a.m. and at midnight: the mix of bacteria and what they're doing shifts over each day.

The **microbiome daily rhythm** is the repeating, roughly 24-hour change in which gut microbes are most abundant, where they sit in the gut, and what chemicals they make, a pattern shaped largely by when the host

eats. (You met the microbiome in Chapter 3.)

The key study is from 2014, when Thaiss and colleagues reported in the journal *Cell* that gut bacteria in both mice and people rise and fall over the day, driven largely by feeding rhythms. In mice, breaking the host's internal clock, either by removing clock genes or by simulating jet lag, scrambled the microbes' rhythm. When the researchers moved microbes from jet-lagged mice or jet-lagged people into germ-free mice (mice raised with no microbes of their own), those mice developed blood-sugar problems and other metabolic changes.

Notice the kind of evidence. The cause-and-effect experiments were all in mice. The human part showed that microbes have daily rhythms and that jet lag changed them in travelers, but the effects of those changed microbes were tested only in mice. The study does not show that jet lag or late nights harm *people* through their microbes. That's why "your microbes follow a daily rhythm" is solid, while "a sleep hack resets your gut bacteria" is not.

Hype Meter: "This sleep hack resets your gut bacteria"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. Gut microbes do have daily rhythms, shown in mice and people (Thaiss 2014), but the experiments linking a disrupted clock to harmful microbe changes were done in mice. No human trial has shown that a sleep trick, supplement, or gadget "resets" the microbiome in a way that improves gut or mental health. **What would change the grade:** Randomized trials in people that change sleep timing, then measure both microbes and real symptoms over months, could move a carefully worded version of this claim to Preliminary.

18.6 Sleep Hygiene: Setting Up the Conditions for Sleep

You can't force sleep, but you can make it easier. **Sleep hygiene** is the set of everyday habits and bedroom conditions that make good sleep more likely, such as a regular schedule, a dark and cool room, and limiting caffeine and screens before bed. ("Hygiene" here just means healthy habits, not cleanliness.)

The CDC's sleep page (dated May 15, 2024) lists tips like these:

- Go to bed and wake up at the same times each day, including weekends.
- Keep the bedroom quiet, relaxing, and cool.
- Turn off electronic devices at least 30 minutes before bed.
- Avoid large meals close to bedtime.
- Limit caffeine in the afternoon and evening.
- Get regular exercise.

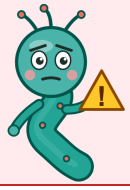
These are reasonable, low-risk habits, but they are not a treatment for a sleep disorder. Ongoing insomnia, loud snoring with pauses in breathing, or gut symptoms that wake you at night are reasons to see a doctor, not just to buy blackout curtains.

Can you catch up on weekends?

Many students treat the weekend like a sleep bank: borrow on weekdays, pay it back Saturday. A 2019 experiment by Depner and colleagues tested a version of this in 36 healthy young adults under controlled conditions. A small control group had nine-hour sleep opportunities. One group had five-hour sleep opportunities for nine nights. Another had five-hour nights during a "workweek," then could sleep as much as they wanted for a weekend, then went back to short nights. Over the weekend, the recovery group slept only about 1.1 hours more in total than at baseline. When short nights resumed, their body clocks were running later, and their insulin sensitivity (how well the body responds to the hormone that controls blood sugar) dropped, just as it did in the group that never got a weekend.

This was a small, short study in adults, and it measured metabolism, not the gut. But it fits a broader point: sleeping in helps you feel less tired without fully erasing a week of short nights, and a later weekend schedule makes Monday harder for a teen body clock.

Don't confuse "feeling rested" with "fully recovered"



A long Saturday sleep can make you feel great, but in the 2019 lab study, the body's response to short nights came right back once the short nights did. A steadier schedule across the whole week works with your body clock instead of against it.

18.7 Moving Your Body: Exercise, Gut Transit, and Mood

Sam runs cross-country, so he's already active. But he has noticed two opposite things: easy runs seem to settle his stomach, while hard race-day efforts sometimes send him sprinting for a porta-potty. Both observations fit the science.

Physical activity is any body movement produced by skeletal muscles that uses energy, from walking to class to running a race. Exercise is the planned, repeated kind. The CDC (page dated December 4, 2025) says children and teens ages 6 to 17 should get 60 minutes or more of moderate-to-vigorous physical activity every day, mostly aerobic activity like walking or running, with vigorous activity, muscle-strengthening, and bone-strengthening activities each on at least 3 days a week.

What exercise does to gut movement

Exercise and gut transit describes how physical activity changes how quickly food and waste move through the digestive tract, along with related changes in blood flow and the gut lining. The relationship depends

heavily on how hard and how long you exercise.

At moderate levels, being more active seems to help IBS. In a 2011 randomized trial, Johannesson and colleagues assigned 102 adults with IBS either to increase their physical activity, with instructions from a physical therapist, or to keep their usual lifestyle. Seventy-five people finished. On a standard IBS symptom severity score, the typical (median) improvement was 51 points in the activity group, compared with 5 points in the control group. That is one trial, in adults, but it was randomized, which makes it stronger than a survey.

At the extreme, the picture flips. A 2017 systematic review by Costa and colleagues described "exercise-induced gastrointestinal syndrome." The review found that as exercise gets harder and longer, signs of injury to the gut lining rise, the lining becomes leakier, and strenuous exercise can slow stomach emptying and small intestine transit and reduce absorption. Exercising for two hours or more at about 60% of maximum aerobic capacity seemed to be the point where significant gut disturbances appear, whatever a person's fitness level. Heat and running made it worse. These changes reversed after exercise, and the review noted that moderate exercise appears to benefit people with IBD and IBS, while the safety of very strenuous exercise for them hasn't been studied enough.

So Sam's two experiences aren't contradictory. Easy, regular movement and an all-out race are different signals to the gut.

What exercise does for mood

Exercise and mood refers to the effects of physical activity on emotional well-being, including symptoms of depression, anxiety, and stress. Here the evidence is unusually large. In 2023, Singh and colleagues published an "umbrella review" in the *British Journal of Sports Medicine*, combining 97 reviews that covered 1,039 trials and 128,119 adult participants. Physical activity programs had medium-sized benefits for symptoms of depression and anxiety compared with usual care, and higher-intensity activity was linked to larger improvements. One caution: 77 of the 97 included reviews were rated "critically low" quality on a standard checklist for judging reviews, and all participants were adults. Part of the reason is hard to avoid: people always know whether they are exercising, so trials can't hide which group someone is in, and expectations may inflate the results. For young people, a 2023 meta-analysis in *JAMA Pediatrics* (Recchia and colleagues) pooled 21 trials with 2,441 children and teens (average age 14) and found that physical activity programs reduced depressive symptoms, by a smaller amount than in the adult reviews.

Hype Meter: "Exercise helps with depression and anxiety symptoms"

Strong	Moderate	Preliminary	Hype

Verdict: Strong. A 2023 umbrella review combined 97 reviews of more than 1,000 randomized trials with over 128,000 adults and found medium-sized improvements in depression and anxiety symptoms from physical activity programs. The benefit shows up again and again across populations, which is why the grade is Strong. But most of the reviews had serious quality problems, trial participants can't be blinded, and a 2023 analysis of 21 trials in children and teens found a smaller benefit than in adults, so the exact size of the effect, especially for teens, is less certain than the direction. **What would change the grade:** Very little would move it down; large, high-quality trials in teens would make the evidence even more direct for this book's readers. Exercise is a support, not a replacement for other treatment when someone has depression.

Does exercise help mood through the microbiome?

Here's where wellness posts take a leap: exercise changes your gut bacteria, and those bacteria improve your mood. Each step sounds plausible.

In 2018, Allen and colleagues had 32 previously inactive adults (18 lean and 14 with obesity) do supervised endurance exercise three days a week for six weeks. Their gut microbes changed, and in lean participants the microbes made more short-chain fatty acids, molecules you met in Chapter 6. But the changes depended on body weight and were "largely reversed" after six weeks without exercise. And the study did not measure mood at all.

Hype Meter: "Exercise changes your microbiome in ways that improve your mood"

Strong	Moderate	Preliminary	Hype

Verdict: Hype. Exercise does change gut microbes in people, but in the key human study (32 adults, 6 weeks), the changes were small, depended on body weight, mostly disappeared after stopping, and mood was not measured. No human study has shown that these microbe changes are *why* exercise helps mood. The mood benefit itself is Strong; the microbiome explanation is a popular story that the evidence does not yet support. **What would change the grade:** Studies that measure microbes and mood together, first in animals and then in people over months, and test whether blocking the microbe change also blocks the mood benefit, could move a carefully worded version of the link to Preliminary.

18.8 Therapy for the Gut-Brain Axis

When Sam's gastroenterologist first suggested he see a psychologist, his stomach dropped for a different reason. "So she thinks I'm making it up," he told Riya. Many patients worry about the same thing.

Psychotherapy is treatment that uses structured conversations and practice with a trained professional, such as a psychologist or licensed counselor, to change patterns of thinking, feeling, behavior, and body responses. It's often called talk therapy, but it usually includes practicing skills between sessions.

The best-studied type is cognitive behavioral therapy (CBT), which helps people notice how thoughts, behaviors, and body sensations feed each other, and practice new responses. CBT has strong evidence for mental health conditions. A 2023 meta-analysis by Cuijpers and colleagues combined 409 trials with 52,702 patients and found that CBT clearly helped depression compared with control conditions, including in children and adolescents (with a smaller effect than in adults). A 2025 analysis by Hofmann and colleagues of 49 randomized trials found a medium-sized benefit of CBT for anxiety disorders compared with placebo-type control conditions.

Therapy built for the gut

Brain-gut psychotherapy is the family of psychological treatments designed specifically for gut conditions, which target the gut-brain axis directly: how the brain processes gut signals, how stress and worry change gut function, and how fear of symptoms leads to avoidance. A 2022 report from a Rome Foundation working team, led by Keefer, calls these "brain-gut behavior therapies" and reviews five classes of them, including gut-focused CBT and gut-directed hypnotherapy.

Why would talking change a gut? Recall from Chapter 8 that in IBS the gut's pain signals can be amplified, like a smoke alarm set too sensitive, and from Chapter 7 that stress hormones and nerves change gut movement and sensitivity. Brain-gut psychotherapy works on the brain end of that loop. It doesn't mean the pain started in the mind. It means the brain is one of the places where the volume knob sits.

Two approaches have the most evidence for IBS:

- **Gut-focused CBT.** Patients learn how the gut-brain axis works, track symptoms and their triggers, practice muscle relaxation, learn to handle worry about symptoms, and gradually stop avoiding situations (like long bus rides) out of fear of an attack.
- **Gut-directed hypnotherapy.** A trained therapist guides the patient into a deeply relaxed, focused state and uses imagery and suggestions about gut comfort, for example picturing the gut as a calm, smoothly flowing river. Patients usually also practice at home with recordings. This is not stage hypnosis; it is a guided, cooperative form of focused relaxation.

How well do they work? In 2020, Black and colleagues published a network meta-analysis in the journal *Gut*, combining 41 randomized trials with 4,072 people with IBS. Compared with control conditions, several therapies lowered the chance of still having symptoms after treatment: self-guided or minimal-contact CBT (relative risk 0.61), face-to-face CBT (0.62), and gut-directed hypnotherapy (0.67). A relative risk of 0.67 means the chance of remaining symptomatic was about a third lower. But the authors warned that most trials had a high risk of bias, partly because patients always know whether they are getting therapy, so the benefits were "likely to have been overestimated." No therapy was clearly better than the others.

Guidelines now include these therapies. The American College of Gastroenterology's 2021 IBS guideline suggests gut-directed psychotherapy for overall IBS symptoms. For children and teens, a 2025 guideline from the European and North American pediatric gastroenterology societies (ESPGHAN and NASPGHAN), covering ages 4 to 18, recommends hypnotherapy (strong recommendation, moderate-certainty evidence) and CBT (strong recommendation, low-certainty evidence) as treatment options for IBS and related abdominal pain conditions.

Hype Meter: "CBT and gut-directed hypnotherapy help IBS symptoms"

Strong	**Moderate**	Preliminary	Hype

Verdict: Moderate (near the top of the range). A 2020 network meta-analysis of 41 trials with 4,072 people found that CBT and gut-directed hypnotherapy reduced the chance of ongoing IBS symptoms, and a large 2018 trial of 436 adults found lasting benefits from home-based CBT. The ACG's 2021 guideline suggests gut-directed psychotherapy (a conditional recommendation), and a 2025 pediatric guideline recommends hypnotherapy and CBT. The grade stops short of Strong because many trials had a high risk of bias and the true benefit is probably smaller than reported. **What would change the grade:** More large trials with strong control conditions (for example, comparing therapy with an equally engaging education program) and long follow-up could move it to Strong. These therapies help many people; they don't cure IBS.

A closer look at one trial

The biggest single trial of CBT for IBS is the IBS Outcome Study (IBSOS). In 2018, Lackner and colleagues randomly assigned 436 adults with IBS whose symptoms hadn't improved with usual care to one of three groups: standard CBT (10 weekly one-hour clinic sessions), minimal-contact CBT (4 sessions, mostly home study using the same skills), or 4 sessions of IBS education about stress, diet, and lifestyle. Two weeks after treatment, 61.0% of the minimal-contact CBT group rated their gut symptoms as moderately or substantially improved, compared with 43.5% of the education group. Six months later, gastroenterologists who didn't know which group a patient was in rated 58.4% of the minimal-contact CBT group as improved, compared with 44.8% of the education group. The shorter, home-based version worked about as well as the full clinic version.

How to read a gut-brain claim: the 2018 IBSOS trial of CBT for IBS

Question	This study
Mouse or human?	Human: 436 adults with IBS (average age about 41, 80% women) at two US medical centers. No teens.
Correlation or cause?	Cause, within limits. People were randomly assigned to groups, so differences in improvement can be credited to the treatment. Patients knew which treatment they got, but one outcome was rated by gastroenterologists who did not.
How many?	436 people, large for a therapy trial (about 145 per group).
How long?	Outcomes were measured 2 weeks, 3 months, and 6 months after treatment ended.
Who paid for it?	The US National Institutes of Health (NIDDK grant 77738). The paper reports no conflicts of interest.
Is something being sold?	No product is sold through the study. The home-study materials were based on a self-help workbook co-written by the lead researcher, a detail worth noting even though no conflict was reported.

The conclusion: this is strong evidence that a brief, mostly at-home CBT program helps many adults with stubborn IBS more than education alone. It doesn't show that everyone benefits (about 4 in 10 in the CBT group did not rate themselves much improved), and it doesn't directly test teenagers.

18.9 Mindfulness, Slow Breathing, and Heart Rate Variability

Mindfulness is the practice of paying attention to the present moment, including thoughts and body sensations, on purpose and without judging them. In a gut condition, that might mean noticing a cramp as a sensation ("tightness, lower left, about a 4 out of 10") instead of spiraling into a story ("this is going to be a disaster, I'll have to leave class").

How strong is the evidence? In 2014, Goyal and colleagues reviewed 47 trials with 3,515 participants for the journal *JAMA Internal Medicine*. Mindfulness meditation programs produced small-to-moderate improvements in anxiety, depression, and pain, but no evidence that they worked better than other active treatments like exercise or therapy. The evidence for effects on sleep, attention, and positive mood was low or insufficient. For apps, a 2024 meta-analysis by Linardon and colleagues of 45 randomized trials found that mindfulness apps produced small improvements in depression and anxiety symptoms compared with control groups, with no clear advantage over other active treatments. Small and real is a fair summary. "Proven cure" is not.

Breathing and the vagus nerve

Slow breathing is deliberately breathing at a slower-than-usual pace, often around six breaths per minute, with longer, steady exhales. You can try it right now: breathe in gently for about four seconds and out for about six. Six breaths like that take about a minute.

Why might it matter for the gut-brain axis? It connects to a measurement called heart rate variability. **Heart rate variability** (HRV) is the natural variation in the time between one heartbeat and the next. A healthy heart is not a metronome: when you breathe in, your heart speeds up slightly, and when you breathe out, it slows, largely because the vagus nerve, Vee's home from Chapter 2, puts the brakes on the heart during the exhale. One part of HRV, often called vagally mediated HRV, is used by researchers as a window into how active the parasympathetic "rest and digest" system is.

In 2022, Laborde and colleagues published a meta-analysis of 223 studies of voluntary slow breathing. Vagally mediated HRV went up during slow-breathing sessions, right after a single session, and after training programs with many sessions. A companion review by Sevoz-Couche and Laborde explained that breathing near a "resonant" rate of about 0.1 cycles per second, which works out to about six breaths per minute, seems to produce the biggest effect.

What slow breathing does and doesn't show



When you breathe out slowly, my branches to the heart get busier, and HRV goes up. That's solid physiology. But higher HRV during a breathing exercise is not the same as "fixing" your gut, so think of slow breathing as a free, low-risk way to turn down the stress dial, not a cure.

There's no strong evidence that slow breathing on its own treats IBS or IBD. It's commonly taught as one skill inside CBT and hypnotherapy, and Sam uses it before races. Its strengths are that it's free, fast, and safe for most people.

18.10 Being Your Own Observer: Self-Monitoring and Behavior Change

Self-monitoring is regularly recording your own symptoms, behaviors, and circumstances (such as sleep, stress, food, activity, and bowel habits) to notice patterns and share accurate information with your care team. It's a core part of gut-focused CBT; the IBSOS trial included self-monitoring of symptoms, their triggers, and their consequences. Doctors also sometimes suggest food or symptom diaries.

But a diary can mislead. Here are the traps:

1. **Small samples.** A week has seven data points. One weird day (a stomach bug, a test, a birthday dinner) can create or erase an apparent pattern.

2. **Confounders.** A confounder is a third factor that affects both things you're comparing. If Sam sleeps badly *because* he's stressed, and stress also flares his IBS, sleep and gut symptoms will move together even if sleep itself does nothing to his gut.
3. **Reverse direction.** Maybe gut pain the night before woke him up, so bad gut days cause bad sleep, not the other way around.
4. **Expectation.** If Sam believes poor sleep wrecks his gut, he might notice and rate symptoms more harshly after a bad night.

Behavior change is the process of adopting and keeping a new health habit, such as a steadier bedtime or regular activity, usually by setting small, specific goals, tracking them, and adjusting based on what you learn. It pairs well with self-monitoring: change one thing at a time, keep it going long enough to see a pattern, and compare with before. A "new me" plan that changes sleep, food, exercise, and screens on the same Monday is hard to keep, and if it works, you won't know which part did it.

If you're going through this

If you track your symptoms, try to keep it short and kind, a minute or two a day, so it doesn't become another source of worry. Bring the log to appointments; patterns like "pain wakes me up at night" or "symptoms are worse the week of exams" help your care team. If tracking starts making you more anxious or makes you avoid food or activities you used to enjoy, that's worth telling your doctor or therapist too. Your diary is a tool for questions, not a verdict on your body.

The MicroSim below lets you practice this kind of careful self-observation with a week of made-up data.

Diagram: Gut and Sleep Diary



Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch18-gut-sleep-diary/main.html

Open the Gut and Sleep Diary fullscreen

MicroSim specification: Gut and Sleep Diary

Type: microsim **sim-id:** ch18-gut-sleep-diary
Library: p5.js
Status: Implemented
Bloom Level: Evaluate
Bloom Verb: judge
Learning Objective: The learner will record or explore a one-week diary of sleep, stress, and gut symptoms, interpret the correlation between sleep and symptoms, and judge the limits of that personal data (small samples, confounders, reverse direction).

Canvas: 450 px drawing area plus 150 px controls (iframe 602 px); responsive to about 380 px wide.

Controls: Day select (Mon to Sun); sliders for Sleep (3 to 11 hours, step 0.5), Stress (0 to 10), and Gut symptoms (0 to 10); Load sample data, Clear all, and Show stress line checkbox.

Rules: Moving a slider records that value for the selected day. The sim computes the Pearson correlation (r) between sleep and gut symptoms and between stress and gut symptoms, using only logged days (at least 3 needed). It always shows a small-sample warning with the number of days, and it shows a confounder warning when stress tracks both sleep and symptoms (|r| of at least 0.5 for both).

Privacy: Data lives only in the page's memory. Nothing is stored or sent; reloading erases it.

Provenance: Section 18.10. The preloaded week is fictional practice data, labeled as such. Correlation strength wording is a teaching convention.

Start with the **sample data**: a made-up week for Sam. Look at the time chart first, then the scatter plot. You should see a strong negative correlation: on nights with less sleep, gut symptom scores were higher. Now turn on **Show stress line**. Stress climbs on exactly the days sleep drops, and the confounder warning appears. With this data, you can't tell whether sleep, stress, or both drive Sam's symptoms.

Next, experiment. Select Wednesday (the test day) and change its gut score from 7 to 2. Watch how much r changes from a single day. Then try **Clear all** and enter your own week, or an imaginary one. Notice that the sim needs at least three days before it will compute anything, and that it never stops warning you about sample size. Your entries stay in this page only: nothing is saved or sent, and reloading the page erases them.

What this model leaves out

- Seven days is far too few to find a reliable personal pattern; real self-monitoring for a care team usually runs for weeks.
- The sim compares same-day values only. Real effects can be delayed (a bad night affecting the next day, or the next week).
- It tracks just three things. Food, meal timing, illness, medicines, periods, and other factors are confounders it can't see.
- The 0 to 10 scores are self-ratings, which are shaped by mood and expectations, not objective measurements.
- A correlation in one person's diary can't show cause; only changing one thing at a time, over enough time, and ideally with your care team, gets closer to that.

At the Bedside: Sam's Course of Brain-Gut Therapy

Meet the patient (fictional)

Sam is 16 and runs cross-country. He was diagnosed with IBS with mixed bowel habits at 15, after tests ruled out other causes. Diet changes and medicine from his gastroenterologist helped some, but cramps and urgent trips to the restroom still spike before big tests and races. He has started skipping team bus trips and asking to take tests in a room near the restroom. He tells his doctor he's afraid the pain will "never go away."

What the doctor checks: His gastroenterologist reviews his history and confirms nothing has changed that would suggest a different diagnosis, such as weight loss, blood in the stool, or symptoms waking him at night (these "red flags" would prompt more testing). She looks at Sam's two-week symptom diary, asks about sleep, mood, school stress, and how much the symptoms are limiting his life, and screens for anxiety and depression with a short questionnaire.

Connecting the signals: Sam's diary shows symptoms clustering around tests, races, and short nights. His gut is sensitive (Chapter 8), stress shifts gut movement (Chapter 7), worry about symptoms adds more stress before each event, and avoidance is shrinking his life. These are exactly the loops brain-gut psychotherapy targets.

Diagnosis: IBS with mixed bowel habits, with test anxiety and symptom-related avoidance. Nothing new or dangerous.

Why it happens: In IBS, signals from the gut are amplified on their way to the brain, and the brain's stress response feeds back to make the gut more reactive. Poor sleep and stress may turn the sensitivity up further, though in Sam's case it's hard to tell which comes first.

The mind-body side: Sam's first reaction to the referral was, "So it's all in my head?" His doctor explains that his pain is real and that therapy works on the brain's side of the two-way gut-brain connection, much as physical therapy retrains muscles after an injury. Over 10 weeks with a psychologist trained in brain-gut therapy, Sam learns how the gut-brain axis works, keeps a short daily log, practices slow breathing and muscle relaxation, and learns to answer catastrophic thoughts with more realistic ones. He also does a short course of gut-directed hypnotherapy with home recordings. What improved: fewer pain days, less fear before tests, and he rides the team bus again. What didn't: he still has some urgent mornings before big races, and a stomach bug in week 6 set him back for a while. His sleep improved only a little, because cross-country meets and homework still keep him up late.

Treatment today: IBS care usually combines education, attention to diet and lifestyle, medicines aimed at specific symptoms when needed, and brain-gut psychotherapy such as CBT or gut-directed hypnotherapy, which the 2021 American College of Gastroenterology guideline suggests for overall IBS symptoms and a 2025 pediatric guideline recommends for children and teens. Treatment plans are individual and are decided with the care team.

What's new in research: In 2026, a Dutch randomized trial in the *British Journal of General Practice* tested home-based guided hypnotherapy through a website for 152 children aged 7 to 17 with IBS or functional abdominal pain seen by family doctors. At 12 months, adequate relief was high in both groups and not significantly different (79.5% with hypnotherapy vs 74.3% with usual care alone), but the hypnotherapy group had relief more often at 3 and 6 months and reported less pain. **Evidence grade: Preliminary.** It's one trial, and its main 12-month result showed no difference, but it suggests online hypnotherapy might speed relief for kids without access to a therapist.

Your turn: reason through a variation

Riya's Crohn's disease is in remission, but she has started feeling anxious and sleeping badly before every orchestra concert, and she wonders if CBT would "fix" her Crohn's the way it helped Sam's IBS. How would you reason about this?

Answer: CBT and other brain-gut therapies can help Riya with anxiety, sleep, and coping, and many IBD care teams include psychologists for exactly that. But Crohn's disease is driven by immune inflammation, so therapy is not a replacement for her biologic medicine or monitoring by Dr. Alvarez. Since poor sleep in people with Crohn's in remission has been linked to later flares (an association, not proof of cause), improving her sleep and stress is a reasonable thing to discuss with her care team as one part of her plan.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: You can fully catch up on lost sleep by sleeping in on weekends.
Reality: Sleeping in helps you feel less tired, but in a 2019 lab study, the body's metabolic response to short

nights returned as soon as short nights resumed after a weekend of recovery sleep. Weekend sleep-ins also push teen body clocks later, making Monday harder.

Myth: Any amount or intensity of exercise is equally good for gut symptoms.
Reality: Regular moderate activity improved IBS symptoms in a randomized trial, but very long, hard exercise (around two hours or more at high effort) can slow parts of the gut, irritate the gut lining, and trigger symptoms. Intensity and duration matter.

Myth: If a doctor recommends therapy for IBS, it means the pain is psychological or fake.
Reality: IBS pain is real and comes from the gut-brain axis. Brain-gut psychotherapy works on the brain's side of that two-way loop, changing how gut signals are processed and how stress affects the gut, and guidelines recommend it alongside other care.

Myth: Mindfulness apps are proven cures for gut and mood problems.
Reality: Mindfulness programs and apps give small, real improvements in anxiety and depression symptoms in trials, but they haven't been shown to beat other active treatments, and they don't cure IBS or IBD.

Myth: If your symptom diary shows a pattern, you've found the cause.
Reality: A week or two of personal data is a small sample, and confounders (like stress affecting both sleep and symptoms) or reverse causation can create patterns. A diary is great for generating questions to test with your care team.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Science proves working out rebuilds your gut microbiome and that's why it cures anxiety. Six weeks, new gut, new you!"

Grade: Hype. Exercise does improve anxiety and depression symptoms on average (Strong evidence from many trials), but that's not a cure. Exercise also changes gut microbes, but in the key study of 32 adults, the changes were small, depended on body weight, and largely reversed six weeks after stopping, and the study didn't measure mood. No human study shows microbes are the reason exercise helps anxiety. A careful version: "Regular exercise helps many people's mood, and it changes gut microbes a little; scientists don't know yet whether those two facts are connected."

2. Predict: Riya practices violin until 1 a.m. every night for two weeks before a concert. Based on the research in this chapter, what might you predict about her Crohn's disease, and how confident should you be?

In a large study, people with Crohn's in remission who reported poor sleep had about twice the odds of active disease six months later. So it's reasonable to predict a somewhat higher chance of a flare in the following months if poor sleep becomes a pattern. But confidence should be modest: the study showed an association, two weeks is short, and concert stress could matter as much as sleep. She should keep taking her medicine and tell Dr. Alvarez if symptoms change.

3. Explain: Sam slows his breathing to about six breaths per minute before a race. Explain what happens to his heart rate variability and why, using the vagus nerve.

During slow breathing, the heart speeds up a bit on each inhale and slows on each long exhale. That slowing comes mostly from the vagus nerve's "brake" on the heart, which is part of the parasympathetic system. Slower, deeper breaths make these swings larger, so vagally mediated HRV goes up, which a 2022 meta-analysis of 223 studies confirmed. This shows parasympathetic activity increasing, which may help Sam feel calmer, but it doesn't directly prove any change in his gut.

4. Apply: A school is debating whether to move its start time from 7:30 a.m. to 8:30 a.m. Use this chapter's evidence to write the strongest one-paragraph argument for the change.

Teens need 8 to 10 hours of sleep per 24 hours (AASM 2016), yet in 2025 only about 1 in 4 US high school students got even 8 hours on school nights (CDC). Puberty shifts sleep timing up to 2 hours later, so teens can't simply fall asleep earlier, and the AAP calls start times before 8:30 a.m. a key, changeable cause of teen sleep loss. Better sleep may also matter for students with chronic conditions, since poor sleep has been linked to later flares in Crohn's disease.

5. Read the data. In the 2018 IBSOS trial (Lackner et al., *Gastroenterology*), 436 adults with IBS were randomly assigned to standard CBT (10 clinic sessions), minimal-contact CBT (4 sessions, mostly at home), or IBS education (4 sessions). Here are the percentages rated "moderately or substantially improved" for two of the groups:

Time and rater	Minimal-contact CBT	Education
2 weeks after treatment, rated by patients	61.0%	43.5%
2 weeks after treatment, rated by gastroenterologists	55.7%	40.4%
6 months after treatment, rated by gastroenterologists	58.4%	44.8%

5. What does this data show, and what can't it show?

It shows that more people improved with minimal-contact CBT than with education, by roughly 14 to 18 percentage points, and the difference held for six months even when rated by doctors who didn't know the patients' groups. It also shows that many people improved with education alone (over 40%), so some improvement comes from attention, time, and information. It can't show that CBT works for teens (all participants were adults), that it helps everyone (about 4 in 10 didn't improve much), or how long the benefit lasts past six months. A useful follow-up would be a similar randomized trial in teenagers with IBS, with follow-up for a year or more.

Exercises

Remember

1. How many hours of sleep per 24 hours does the American Academy of Sleep Medicine recommend for teens aged 13 to 18?

Answer

8 to 10 hours per 24 hours on a regular basis (Paruthi et al., 2016).

1. Name the two brain-gut psychotherapies with the most evidence for IBS.

Answer

Gut-focused cognitive behavioral therapy (CBT) and gut-directed hypnotherapy.

Understand

1. Explain why the Thaiss 2014 study supports "gut microbes have a daily rhythm" but not "late nights harm people through their microbes."

Answer

The study showed daily microbe rhythms in both mice and people. But the experiments showing that a disrupted clock leads to harmful microbe changes, with effects passed on by transferring microbes, were done in mice, so they can't tell us what happens in people.

1. Explain how a confounder could make sleep and gut symptoms look connected in a personal diary even if sleep has no effect on the gut.

Answer

A third factor, such as stress, could cause both poor sleep and worse gut symptoms. Then sleep and symptoms would rise and fall together because both follow stress, not because one causes the other.

Apply

1. Using the Gut and Sleep Diary MicroSim, load the sample data and record the sleep-symptom r. Then change one day's values to make the pattern disappear. How many days did you have to change? What does this tell you about drawing conclusions from one week?
2. A friend with IBS is training for a half marathon and says, "Exercise is good for IBS, so the harder I train, the better my gut will be." Use the evidence on exercise and gut transit to give your friend accurate advice that doesn't tell them what to do medically.

Analyze

1. Compare the Ananthakrishnan 2013 Crohn's study and the Buchanan 2014 IBS study. For each, describe the population, size, and type of evidence, and explain why one finding might apply more confidently to Riya than the other applies to Sam.
2. In the IBSOS trial, more than 40% of the education group improved. Analyze at least three reasons people in a "control" group might improve, and explain why this makes randomized comparison groups so important.

Evaluate

1. An app advertises: "Our 5-minute daily breathing exercise is clinically proven to raise your vagal tone and heal your gut." Evaluate each part of this claim using the slow breathing and HRV research in this chapter. Which parts are supported, and which are not?
2. Some people argue that teens should treat sleep hygiene, exercise, and mindfulness as their "first-line treatment" for IBS before trying anything else. Judge this position using evidence from this chapter and the treatments discussed in Chapter 10. What would you keep, and what would you change?

Create

1. Design a four-week self-monitoring plan that would help Sam test whether sleep affects his gut symptoms more fairly than his phone notes did. Specify what he records, how he would deal with stress as a confounder, and what result would (and wouldn't) convince you.

2. Create a one-page "brain-gut therapy explainer" for a teen who has just been referred to a psychologist for IBS and is worried it means "it's all in my head." Use at least three facts from this chapter and keep it under 250 words.

Key Takeaways

- Circadian rhythms run on a roughly 24-hour clock set mostly by light (in the brain) and meal timing (in the gut); puberty shifts teen sleep timing up to 2 hours later.
- Sleep cycles through light, deep, and REM stages; teens need 8 to 10 hours per 24 hours, but in 2025 only about 1 in 4 US high school students got 8 hours on school nights.
- Disturbed sleep is linked to slightly higher inflammation markers, and in people with Crohn's in remission, poor sleep was linked to twice the odds of a flare six months later (an association, not proof of cause).
- Gut microbes follow a daily rhythm; the cause-and-effect evidence about disrupted clocks and microbes comes from mice, so "sleep hacks reset your microbiome" is Hype.
- Moderate, regular activity helped IBS symptoms in a randomized trial and helps depression and anxiety symptoms (Strong), while very long, hard exercise can disturb the gut. The idea that exercise lifts mood *through* microbes is not supported yet (Hype).
- Brain-gut psychotherapies such as CBT and gut-directed hypnotherapy reduce IBS symptoms for many people and are recommended by guidelines; therapy for IBS does not mean the pain is fake.
- Slow breathing raises vagally mediated heart rate variability; mindfulness gives small real benefits; and personal diaries are best used to generate questions, because small samples and confounders can fool you.

You've learned to read your own data like a scientist



You can now explain how sleep, movement, breathing, and therapy reach the gut-brain axis, and you know why a week of diary data asks questions instead of answering them. Next, in Chapter 19, we'll leave the lab and go to the dinner table, to talk about culture, family, food, and the stigma that can make gut and mental health harder to talk about.

Quiz: Sleep, Exercise, and Therapy

Test your understanding of Chapter 18. Choose the best answer, then click **Show Answer** to check.

Question 1

How much sleep does the American Academy of Sleep Medicine recommend for teenagers aged 13 to 18?

A. 6 to 7 hours per night

B. 8 to 10 hours per 24 hours

C. 7 or more hours per night, the same as adults

D. 11 to 13 hours per 24 hours

Show Answer

The correct answer is **B**. The 2016 AASM consensus recommends 8 to 10 hours per 24 hours for teens 13 to 18. Option C is the adult recommendation; teens need more.

Concept Tested: Teen Sleep Need **Bloom's Level:** Remember

Question 2

Which part of the brain acts as the body's master clock, receiving light information directly from the eyes?

A. The pineal gland

B. The brainstem's vagus nerve nucleus

C. The enteric nervous system

D. The suprachiasmatic nucleus of the hypothalamus

Show Answer

The correct answer is **D**. The suprachiasmatic nucleus (SCN) receives light signals from the eyes and sets the body's circadian rhythm. The pineal gland (A) makes melatonin, but it takes its timing signals from the SCN.

Concept Tested: Circadian Rhythm **Bloom's Level:** Remember

Question 3

What is heart rate variability (HRV)?

A. The natural variation in the time between one heartbeat and the next

B. How fast your heart beats during hard exercise

C. The difference between your resting heart rate and your maximum heart rate

D. An irregular heartbeat that always signals heart disease

Show Answer

The correct answer is **A**. HRV is the beat-to-beat variation in timing, and part of it reflects the vagus nerve's braking effect on the heart. Option D confuses normal, healthy variation with an abnormal heart rhythm.

Concept Tested: Heart Rate Variability **Bloom's Level:** Remember

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Question 4

Why can't most teens solve short sleep simply by going to bed at 9:30 p.m.?

A. Teens need less sleep than younger children, so they aren't tired

B. Melatonin stops being made during adolescence

C. Around puberty, sleep timing shifts later by up to about 2 hours, partly because melatonin is released later

D. The suprachiasmatic nucleus stops responding to light in teenagers

Show Answer

The correct answer is **C**. The AAP describes a puberty-related shift in sleep timing of up to 2 hours, with later nighttime melatonin release. Option A is wrong because teens actually need 8 to 10 hours, more than adults.

Concept Tested: Circadian Rhythm **Bloom's Level:** Understand

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Question 5

In the 2013 study of people with inflammatory bowel disease, people with Crohn's disease in remission who slept poorly had about twice the odds of active disease six months later. Which conclusion fits this evidence best?

A. Poor sleep has been proven to cause Crohn's flares.

B. Poor sleep is linked to later flares, but the study can't show whether sleep causes them.

C. Sleep has no connection to Crohn's disease, since the link was not found in ulcerative colitis.

D. Good sleep cures Crohn's disease.

Show Answer

The correct answer is **B**. It was an observational study, so it shows an association. Early inflammation, pain, or stress could disturb sleep and also lead to flares. Option A overstates the evidence by turning a link into proof of cause.

Concept Tested: Sleep and Inflammation **Bloom's Level:** Understand

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Question 6

Which statement best describes how brain-gut psychotherapy helps IBS?

A. It works on the brain's side of the two-way gut-brain loop, changing how gut signals are processed and how stress affects the gut.

B. It proves the pain was imaginary by making it disappear.

C. It replaces all medical care for IBS.

D. It works by changing the gut microbiome directly.

Show Answer

The correct answer is **A**. Therapies like gut-focused CBT and gut-directed hypnotherapy target the brain end of the gut-brain axis; the pain is real. Option B reflects the common myth that therapy means symptoms are "all in your head."

Concept Tested: Brain-Gut Psychotherapy **Bloom's Level:** Understand

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Question 7

Sam, who has IBS, plans a 3-hour hard training run on a hot afternoon. Based on the 2017 review of exercise-induced gastrointestinal syndrome, what is most likely?

A. The long, hard run will settle his gut, since exercise always helps IBS.

B. Exercise has no effect on the gut, so nothing will change.

C. His gut symptoms will be cured for the week.

D. Gut disturbances such as slowed transit and symptoms become more likely, especially with heat and running.

Show Answer

The correct answer is **D**. The review found that exercise of about two hours or more at moderate-to-high effort can disturb the gut, and heat and running made it worse. Option A ignores that intensity and duration matter: moderate activity helped IBS in a trial, but extreme effort is different.

Concept Tested: Exercise and Gut Transit **Bloom's Level:** Apply

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Question 8

Maya's one-week diary shows that her worst stomachache days followed her shortest nights, and that her stress ratings were also highest on those days. What is the best next step for interpreting her data?

A. Conclude that short sleep causes her stomachaches.

B. Delete the stress ratings because they make the pattern confusing.

C. Keep tracking longer, try changing one thing at a time, and treat stress as a possible confounder to discuss with her care team.

D. Conclude that her stomachaches are caused only by stress.

Show Answer

The correct answer is **C**. One week is a small sample, and stress could drive both poor sleep and symptoms. Longer tracking and one-change-at-a-time testing get closer to an answer. Options A and D both jump from a correlation to a single cause.

Concept Tested: Self-Monitoring **Bloom's Level:** Apply

Question 9

In the IBSOS trial, 61.0% of the minimal-contact CBT group and 43.5% of the education group rated their IBS as moderately or substantially improved two weeks after treatment. What does the education group's result tell you?

A. Education is useless for IBS.

B. Many people improve with attention, information, and time, so a comparison group is needed to see what CBT adds.

C. CBT works for everyone with IBS.

D. The trial was not randomized.

Show Answer

The correct answer is **B**. Over 40% improved with education alone, which shows why randomized comparison groups matter: CBT's real added benefit is the difference between groups. Option C is wrong because about 4 in 10 people in the CBT group did not report much improvement.

Concept Tested: Brain-Gut Psychotherapy **Bloom's Level:** Analyze

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Question 10

A post says: "Exercise rebuilds your microbiome, and that's why it fixes depression." Which analysis matches this chapter's evidence?

A. The mood benefit of exercise is strongly supported, but the claim that it works through microbe changes is not supported by human evidence.

B. Both parts are strongly supported by large human trials.

C. Neither part has any evidence at all.

D. The microbe part is strong, but exercise has no effect on mood.

Show Answer

The correct answer is **A**. A large umbrella review supports exercise for depression and anxiety symptoms, but the key microbiome study had 32 adults, small changes that reversed, and no mood measurements. Option B treats a plausible mechanism as if it were proven.

Concept Tested: Exercise and Mood **Bloom's Level:** Analyze

Chapter 19: Culture, Food, Family, and Stigma

Summary

Gut conditions and mental health conditions are not lived in a lab. They are lived at dinner tables, in classrooms, on team buses, and inside families with their own languages, foods, and beliefs. This chapter explains what stigma is, how it gets inside people's heads, and how it is linked to quality of life and to whether people seek help. It looks at how inflammatory bowel disease has spread around the world and what studies of South Asian migrants show about genes and environment, and it looks at how culture and family shape the way people talk about health, using research on South Asian families as one carefully sourced example. It ends with practical tools: talking with your doctor, getting school accommodations like a 504 plan, finding peer support, and practicing conversations that are both accurate and kind.

Concepts Covered

1. Stigma
2. Self-Stigma
3. Mental Health Stigma
4. Illness Concealment
5. Quality of Life
6. Health Literacy
7. Family Communication
8. Caregiver Role
9. Global IBD Rise
10. Migration and IBD Risk
11. South Asian Health Context
12. Help-Seeking Barriers
13. Talking to Your Doctor
14. School Accommodation
15. 504 Plan
16. Peer Support

Prerequisites

- Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's (what IBD is and how it is treated)
- Chapter 10: IBS and Disorders of Gut-Brain Interaction (what IBS is)
- Chapter 11: Anxiety, Depression, and the Gut (how common anxiety and depression are in gut conditions)
- Chapter 15: Food and Mood (what diet research can and can't show)

The hardest part isn't always the biology



Many teens with gut conditions say the toughest moments aren't the cramps. They're the comments, the awkward silences, and the feeling that you can't mention your bowels or your mood. This chapter is about those moments. We'll check the evidence on stigma and culture the same way we've checked everything else, and then you'll get to practice what to say.

19.1 "Just Eat More Ghee and Stop Worrying"

It's a Sunday dinner at Riya's grandparents' house. The table is full: dal, rice, roti, a vegetable dish Riya helped her grandmother make that afternoon. Riya's aunt, visiting from out of town, watches her push some food around her plate. "You're too thin," she says, loudly enough for everyone to hear. "You just need to eat more ghee and stop worrying so much. In our day, nobody had this Crohn's business." (Riya and her family are fictional; Riya appears throughout this book.)

Riya feels her face get hot. Her aunt loves her. Her aunt is also wrong: Riya's Crohn's disease is an immune condition, diagnosed at 14 after months of pain and weight loss, and it's treated with a biologic medicine she injects. No food caused it and no food will cure it. But saying "you're wrong" at her grandmother's table feels impossible. Her mom changes the subject. Riya stares at her plate.

How do you answer someone who loves you and is wrong? That question is harder than any diagram in this book. Sam has his own version: his cross-country coach keeps telling him his stomach problems are "just nerves" and that he should "push through." This chapter is about the science behind moments like these, and about practicing better ways through them.

If you're going through this

If someone you love says something about your condition that hurts or isn't true, it's normal to freeze, get angry, or go quiet; none of those reactions make you a bad person. You don't have to win every conversation, especially at the dinner table. It can help to pick one trusted adult (a parent, your doctor, a school counselor) who can back you up with facts, so you aren't carrying every explanation alone.

19.2 What Stigma Is, and How It Gets Inside

Imagine someone sticks a note on your back that says "dirty" or "weak" or "faking." Other people read it and treat you differently. That's bad enough. Now imagine that after a while, you start to believe the note yourself. That two-step picture is how psychologists describe stigma.

Stigma is a set of negative beliefs and reactions that leads people to label, judge, and treat others as less worthy because of a trait, such as a health condition. In a widely cited 2002 paper, the researchers Corrigan and Watson broke stigma into three parts:

Part of stigma	What it is	Example with a gut condition
Stereotype	A belief about a group	"People who keep running to the bathroom are gross"
Prejudice	Agreeing with the stereotype and feeling negatively about it	Feeling disgust or annoyance toward a classmate with IBD
Discrimination	Acting on the prejudice	Refusing a restroom pass, mocking someone, leaving them out

Corrigan and Watson described two forms. Public stigma is how the general public reacts to a group. **Self-stigma** is what happens when a person with a condition turns those negative beliefs on themselves ("I'm disgusting," "I'm weak," "I'm a burden"), which can lower self-esteem and confidence.

Mental health stigma is stigma directed at people with mental health conditions or at the act of seeking mental health care, such as the belief that people with depression are weak or that seeing a therapist means you're "crazy." Gut conditions often carry a double load: stigma about bowels and bathrooms, plus stigma about anxiety or depression, which are common in people with IBD and IBS (see Chapter 11).

Why does a neuroscience book care? Because stigma isn't just hurt feelings. It changes behavior, and behavior changes health, as the next sections show.

19.3 Stigma in Gut Conditions: Hiding, Coping, and Quality of Life

In many classrooms, just saying the word "diarrhea" gets a laugh. Gut conditions involve body functions that many cultures treat as private or embarrassing, which leaves plenty of room for stigma.

How common is it? In 2009, Taft, Keefer, and colleagues surveyed 211 adults with inflammatory bowel disease (156 with Crohn's disease and 55 with ulcerative colitis). Eighty-four percent reported feeling stigmatized because of their disease. People who perceived more stigma had worse quality of life, more psychological distress, lower self-esteem, and slightly lower rates of taking their medicines as prescribed, even after accounting for how sick they were.

Quality of life is a person's overall sense of well-being across the parts of life that matter to them, including physical health, emotions, relationships, school or work, and daily activities. Health researchers often measure "health-related quality of life" with questionnaires that ask how a condition affects these areas. In the Taft study, perceived stigma explained 10% to 22% of the differences in health-related quality of life scores between people. The authors called these effects small, but comparable to other patient factors that researchers more commonly measure.

A 2016 systematic review by Taft and Keefer pulled together research on IBD stigma and described three angles: how people perceive stigma, whether they internalize it (self-stigma), and whether they actually experience discrimination. They concluded that stigma may affect quality of life, mental health, and medication use, and that research on it still has major gaps.

Hiding symptoms

One of the most common responses to stigma is hiding. **Illness concealment** is keeping a health condition or its symptoms secret from others, for example by making up excuses for missed school, skipping meals to avoid bathroom trips, or not telling a doctor about symptoms that feel embarrassing.

Concealment makes sense in the moment; it protects you from awkward questions. But it has costs. If teachers don't know, they can't help. If friends don't know, they may assume you're skipping. And if a doctor doesn't hear about blood in the stool, bathroom trips at night, or low mood, they can't adjust treatment. Hiding symptoms can make a condition harder to treat, which is why the care team's first job is often making it safe to talk.

Here is the study behind this section's key number, checked with our six questions.

How to read a gut-brain claim: the 2009 IBD stigma survey

Question	This study
Mouse or human?	Human: 211 adults with IBD for at least 6 months (156 Crohn's, 55 ulcerative colitis). About 77% were women and about 97% were White; most were recruited online.
Correlation or cause?	Correlation. It was a one-time questionnaire, so it can't show whether stigma worsens quality of life, poor health makes people feel more stigmatized, or both.
How many?	211 people, a moderate number for a survey.
How long?	A single snapshot; no one was followed over time.
Who paid for it?	The full text has no funding statement. It thanks the Crohn's & Colitis Foundation of America for help recruiting participants.
Is something being sold?	No.

The conclusion: stigma is common among adults with IBD and is linked to worse outcomes. But this sample was almost entirely White adults recruited online, so it tells us little about teens or about families like Riya's. That gap is itself a finding: groups that may face the most stigma are often the least studied.

19.4 Mental Health Stigma and Asking for Help

Think about the last time you felt sick and didn't tell anyone. Maybe you didn't want to make a fuss, or you weren't sure it "counted." Now add the fear that someone will think you're weak, dramatic, or "crazy." That's the extra weight mental health stigma adds.

Help-seeking barriers are the obstacles that keep people from getting care when they need it, including stigma, cost, not knowing where to go, long waits, language differences, and worries about privacy or what family and community will think.

Stigma is one of the biggest. In 2015, Clement and colleagues reviewed 144 studies with 90,189 participants about mental health stigma and help-seeking. Stigma had a small-to-moderate negative effect on seeking help, and it was the fourth-highest-ranked barrier overall. The most common stigma barrier was worry about disclosure: who might find out. For this book's readers, the review found that stigma held back some groups more than others, including ethnic minorities, young people, and men.

How big is the need among teens? In the CDC's 2023 Youth Risk Behavior Survey, 39.7% of US high school students reported persistent feelings of sadness or hopelessness. In the 2025 survey, published in October 2026, that figure was 33.3%, about one in three.

The 2025 report also asked students with those feelings whether they had needed counseling or therapy but not gotten it. Overall, 28.8% reported this kind of unmet need. Unmet need was higher among Asian American students (38.4%) and Black students (33.9%) than among White students (27.1%). "Asian American" in that survey is a broad group that includes South Asian students along with many others, and the Asian estimate had a wide margin of uncertainty, but the pattern fits the idea that some communities face extra barriers to care.

If you are struggling right now

If you are thinking about suicide or are in crisis, call or text **988** to reach the 988 Suicide & Crisis Lifeline (in the US), or go to the nearest emergency room. Outside the US, you can find a helpline at findahelpline.com. You can also talk to a parent, school counselor, or doctor.

Asking for help is a skill, not a weakness



I carry signals from the gut to the brain all day, and the brain's job is to respond, not to ignore them. Noticing that you're struggling and telling someone is the same kind of smart signaling, and research shows stigma is what most often gets in the way.

19.5 IBD Around the World: Not a "Western" Disease

Riya's aunt said nobody had "this Crohn's business" in her day. Is she right that IBD is new, or something that only happens in certain places? The research says the story is more complicated than that.

Global IBD rise is the spread of inflammatory bowel disease from a few early industrialized regions to countries around the world over the last century, with rising new cases in many newly industrialized countries. In 2017, Ng and colleagues published a systematic review in *The Lancet* of 147 population-based studies. They found that more than 0.3% of people had IBD in North America, Oceania, and many European countries. In North America and Europe, most studies showed new cases (incidence) holding steady or falling. But since 1990, incidence had been rising in newly industrialized countries in Africa, Asia, and South America. In Brazil, for example, new Crohn's cases rose by about 11% per year and new ulcerative colitis cases by about 15% per year.

In 2025, a team in *Nature* (Hracs and colleagues, part of a global research group) analyzed 522 population-based studies covering 82 regions from 1920 to 2024. They described IBD moving through epidemiologic stages:

1. **Emergence:** few new cases and few people living with IBD.
2. **Acceleration in incidence:** new cases rise quickly, but the total number living with it is still low.
3. **Compounding prevalence:** new cases level off, but the number of people living with IBD keeps climbing, because IBD usually lasts for life and is rarely fatal.

A fourth stage, in which prevalence levels off as the IBD population ages, has been proposed and modeled but not yet observed. Different regions sit at different stages. So Riya's aunt has a point that IBD was less common in many places a few generations ago. What she's missing is that it has been spreading, and that it is now a global disease.

Hype Meter: "IBD only happens in Western countries"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. A 2017 review of 147 studies found rising IBD incidence in newly industrialized countries in Asia, Africa, and South America, and a 2025 analysis of 522 studies across 82 regions showed IBD moving through epidemiologic stages worldwide. IBD was first common in early industrialized regions, but it isn't limited to them. **What would change the grade:** Nothing realistic; the global data are large and consistent. The careful version: "IBD became common first in Western countries and is now rising in many other parts of the world."

What migration studies show

If IBD were purely genetic, moving to a new country shouldn't change your risk much. If environment matters, it should. That makes migrants a natural experiment.

Migration and IBD risk refers to how the risk of developing IBD changes when people move from one country or environment to another, and what those changes suggest about the roles of genes and environment.

The classic studies come from Leicestershire, a county in England with a large South Asian community. In 1992, Probert and colleagues reported on ulcerative colitis there from 1972 to 1989. South Asians had a relative risk of ulcerative colitis of 2.45 compared with Europeans. In the 1980s, yearly new cases per 100,000 people were:

Group in Leicestershire (1980s)	New ulcerative colitis cases per 100,000 per year
Sikh	16.5
Hindu	10.8
Muslim	6.2

Group in Leicestershire (1980s)	New ulcerative colitis cases per 100,000 per year
European	5.3

First- and second-generation South Asians were at similar risk. A 1993 follow-up by the same team looked at how many people were living with each disease and found a split: ulcerative colitis was more common among South Asians than Europeans (135 vs 90.8 per 100,000), but Crohn's disease was *less* common (33.2 vs 75.8 per 100,000).

Notice how careful the claim has to be. These data come from one county, mostly from the 1970s and 1980s. They show that ulcerative colitis, not IBD in general, was higher among South Asians there. And they don't compare migrants with people still living in South Asia. A 2018 review by Misra and colleagues of 33 studies across countries found that South Asian migrants consistently showed higher and more extensive ulcerative colitis than local populations in individual studies from five countries, but when the numbers were pooled, the difference was not statistically significant, partly because the studies varied so much.

Hype Meter: "South Asian migrants in the UK have higher ulcerative colitis rates than their white neighbors"

Strong | **Moderate** | Preliminary | Hype

Verdict: Moderate. Studies in Leicestershire found ulcerative colitis about 2.45 times as common in South Asians as in Europeans in the 1970s and 1980s, and higher, more extensive ulcerative colitis has been reported in several countries. But the data are older and regional, Crohn's disease was actually less common in the same group, and a 2018 pooled analysis wasn't statistically significant. **What would change the grade:** Large, recent, population-wide studies in several countries, reporting Crohn's and ulcerative colitis separately for specific South Asian communities, could move it up or down.

What does this mean for Riya? Not much about her personally, since every individual's risk depends on many things. What it means for her family conversation is useful, though: IBD is not a "foreign" disease, not a punishment, and not caused by abandoning traditional food. Researchers think the environment people live in, along with genes, shapes risk, and no single food or culture explains it. The US National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) says researchers have not found that specific foods cause or worsen Crohn's disease symptoms, though a person's care team may suggest changes that fit their symptoms.

Hype Meter: "Eating more ghee (or any single traditional food) will heal Crohn's disease"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. Crohn's disease is an immune-driven inflammatory condition, and according to NIDDK, researchers have not found that specific foods cause or worsen Crohn's symptoms. No trial has shown that ghee, or any single food from any culture, heals Crohn's. The diet treatment with real evidence is different: a special liquid formula that doctors prescribe for some children with Crohn's (Chapter 9), planned and monitored by the care team. Food still matters for nutrition, growth, comfort, and family connection, and a care team or dietitian can help plan meals that work during flares and remission. **What would change the grade:** Even reaching Preliminary would take controlled studies in people with Crohn's showing that a specific food lowers inflammation on scopes and blood tests compared with a control diet. Moving higher would take large randomized trials.

19.6 Culture, Family, and the South Asian Health Context

Every family has its own unwritten rules about health. In some, you mention a stomachache and get a doctor's appointment. In others, you get a home remedy, a prayer, a lecture, or a change of subject. None of these families is "the right one." But the rules shape what people say out loud.

Family communication is how family members share information, feelings, and decisions with each other, including what topics are open for discussion, who speaks for whom, and how disagreements are handled. In a health crisis, open, honest family communication helps everyone understand the condition and make decisions together.

Caregiver role is the set of responsibilities family members (often parents or grandparents) take on for someone with a health condition, such as managing appointments and medicines, preparing food, giving emotional support, and advocating with schools, along with the stress that can come with it. For teens, the caregiver role often shifts over time: parents start out in charge, and the teen gradually takes on more of their own care.

Riya's grandmother is part of her care team, even though she isn't a doctor. She cooks with Riya, notices when Riya isn't eating, and is the first person Riya told about her anxiety before flares. Her aunt is trying to be a caregiver too; she just has outdated information. Seen that way, the aunt's comment is a caring impulse with a factual error, not an attack.

What research says about South Asian families and mental health

South Asian health context refers to the cultural, family, migration, and health-system factors that can shape how people with roots in South Asia (including India, Pakistan, Bangladesh, Sri Lanka, Nepal, and nearby countries) understand illness, talk about it, and seek care. First, a caution. South Asian communities are enormously diverse, spanning many countries, languages, religions, generations, and incomes. No study

describes "what South Asian families think," and any single family, including Riya's, can look very different from research averages.

With that caution, here is what a few studies report:

- A 2019 literature review by Karasz and colleagues on South Asian immigrant communities in the US described how ideas about what causes mental illness, the stigma of acknowledging it, and acculturation (how people adapt to a new culture over time) all affect whether people get care. The authors called for culturally responsive approaches and pointed to local community organizations as models. The review notes that research in this area is limited.
- A 2017 qualitative study by Islam and colleagues interviewed 10 South Asian youth, aged 15 to 23, in Peel Region near Toronto, Canada. They described pressures from academics and comparisons, conflicts with parents over different cultural values, and family disruptions. Barriers to care included stigma (including worry about what the community would think), few South Asian or youth-focused professionals, long waits, and costs. When shown 22 local mental health resources, they recognized only about a third (36%).
- A 2022 qualitative study by Basri and colleagues interviewed 14 South Asian American college students in Texas. Their themes included family dynamics, cultural dynamics, the campus environment, university resources, and access to help.

These are small studies that describe experiences, not percentages that apply to everyone. The Islam study is Canadian; the other two focus on the US. Still, they line up with the larger Clement review: stigma, worries about disclosure, and not knowing where to go make help harder to reach, and these barriers can weigh more heavily on young people and on minority communities.

A research theme is not a stereotype



"Some South Asian youth in one small study described stigma about mental health" is a careful finding. "South Asian families don't believe in therapy" is a stereotype. Always ask how many people were studied, where, and whether the result fits the specific person in front of you.

These studies also say little about strengths. Many families, South Asian and otherwise, offer deep support through shared meals, multigenerational households, and relatives who show up during hard times. The goal isn't to change a family's culture. It's to connect accurate medical information with the ways that family already shows love.

For families

If someone in your family has a gut or mental health condition, food and advice are often how love gets expressed, and that's a strength. Try asking before advising: "What would help you right now?" Avoid comments about weight, eating, or "worrying too much" at the table, since a teen with IBD may be eating carefully on purpose. If you have questions about remedies from home or about the medicine, bring them to the care team together; doctors can talk through traditional foods and practices and how they fit with treatment.

19.7 Health Literacy and Talking to Your Doctor

Riya's aunt isn't unintelligent. She's working from the information she has. That's a health literacy issue, and it affects everyone, including doctors.

Health literacy is the ability to find, understand, and use health information and services to make decisions for yourself and others. The US government's Healthy People 2030 initiative defines personal health literacy this way, and it also describes organizational health literacy: how well health organizations make it possible for people to find, understand, and use information. In other words, when a family is confused, it's not only their job to learn more. It's also the clinic's job to explain clearly, in the family's preferred language, with time for questions.

Talking to your doctor is the skill of preparing for and taking an active part in medical visits: sharing accurate information, asking questions, and making decisions with your care team. MedlinePlus, from the US National Library of Medicine (updated October 5, 2024), suggests:

- Before the visit, write down your questions and your symptoms, including when they started and what makes them better or worse.
- List every medicine, vitamin, herb, and supplement you take, including home remedies.
- Bring a trusted friend or family member, and ask the office in advance for an interpreter if you need one.
- During the visit, be truthful about your habits and symptoms, even the embarrassing ones.
- Take notes, and keep asking until you understand.

That second bullet matters for families who use traditional remedies. Telling the doctor about a remedy isn't a confession; it's information that helps keep treatment safe. And the fourth bullet is the antidote to illness concealment.

Your doctor has heard it all



Gastroenterologists talk about stool, gas, and bathroom trips all day, so nothing you say will shock them. A useful trick is to write the awkward thing on your phone and show it, or start with "This is embarrassing, but...", which signals that the next part matters.

19.8 School, Accommodations, and Peer Support

School is where stigma and symptoms collide most often: a teacher who won't sign a pass, a test you can't pause, a class full of people who notice every exit.

School accommodation is a change in how a student learns, is tested, or participates in school that removes a barrier caused by a health condition or disability, without lowering what the student is expected to learn. Examples include restroom access, rest breaks, and extra time.

In the US, the main tool for students with chronic conditions like IBD is a **504 plan**: a written plan, developed by the school with the student and their parents or guardians, that lists the accommodations a student with a disability needs to have equal access to education, under Section 504 of the Rehabilitation Act of 1973.

Section 504 is a federal civil rights law that applies to schools receiving federal funding. A December 2024 fact sheet from the US Department of Education's Office for Civil Rights explains that IBD counts as a disability under Section 504 when it substantially limits a major life activity.

The law treats body functions as major life activities too, and the fact sheet names the digestive system, bowel function, and the immune system. A condition that comes and goes, or is in remission, still counts if it would substantially limit those functions when it is active. Even a student who needs no accommodations is protected from disability-based bullying and harassment, such as teasing about restroom trips.

A 504 plan is not the same as an IEP (individualized education program). An IEP is a plan for students who need special education services, under a different federal law, the Individuals with Disabilities Education Act (IDEA). A student whose chronic health problem limits their strength, energy, or alertness and hurts their schoolwork can sometimes qualify for an IEP under IDEA's "other health impairment" category. For students who mainly need fair access, like restroom breaks and stop-the-clock testing, a 504 plan is the usual tool.

According to a 2021 fact sheet from the Crohn's & Colitis Foundation:

- Each school decides eligibility case by case, usually through its 504 coordinator.
- Commonly requested accommodations include unlimited restroom access, "stop-the-clock" testing (pausing a test's timer during a restroom break), making up work missed for appointments or illness without penalty, tutoring after long absences, and full participation in activities even after missed classes.
- The Foundation recommends having a plan in place at the start of every school year, even during remission, because flares are unpredictable.

- A student doesn't have to be failing to qualify; the plan is about access, not grades.
- Plans usually apply in public schools, and in private schools that receive federal funding. The fact sheet advises creating or updating the plan every year, even if nothing about the student's health has changed.
- The student should help choose the accommodations, because someday they'll need to advocate for themselves.

So the myth that teachers "aren't allowed" to make exceptions is backward: with a 504 plan in place, the school has agreed to them. Sam's IBS isn't the same as Riya's IBD, but students with IBS and other conditions can also ask about accommodations; the school decides case by case.

Not doing it alone

Peer support is help and understanding from people who share a similar experience, such as other teens with IBD or IBS, offered through friendships, support groups, online communities, or camps. Peers can offer something doctors and parents can't: "I've been there." The Crohn's & Colitis Foundation lists resources for young people, including Camp Oasis, a summer camp for kids and teens with IBD, and a website for teens with IBD. Online communities can help too, with one caution from earlier chapters: peers are great for support and terrible as a source of medical claims. When someone in a group swears by a supplement or diet, run it through the Hype Meter and talk to your care team.

Sam's cross-country team turned out to be a kind of peer support. When he finally explained his IBS to two teammates, one of them admitted she gets race-day stomach problems too. Now they warm up together near the restrooms, and nobody makes a big deal of it.

19.9 Practicing the Conversation

Knowing the facts is one skill. Saying them out loud, kindly, under pressure, is another. Here are five moves, drawn from the ideas in this chapter, that can help in tough conversations about health:

1. **Start with the relationship.** Acknowledge the care behind the comment ("I know you want me to feel better").
2. **Give one clear fact, not a lecture.** "Crohn's is an immune condition, and my doctor is treating it with medicine."
3. **Offer a role.** Give the person something helpful to do ("Could you help me find recipes that are easy on my stomach during flares?").
4. **Set boundaries calmly, and in private when you can.** "I'd rather not talk about my weight at dinner."
5. **Bring in backup.** A parent, doctor, or counselor can repeat the facts so you aren't the only messenger.

None of these is a magic script. Sometimes the best choice in the moment is to say nothing and talk later. The MicroSim lets you try different responses and see how each might land.

Diagram: Conversation Practice



Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch19-conversation-practice/main.html

Open the Conversation Practice fullscreen

MicroSim specification: Conversation Practice

Type: microsim **sim-id:** ch19-conversation-practice
Library: p5.js
Status: Implemented
Bloom Level: Apply
Bloom Verb: use
Learning Objective: The learner will use supportive, accurate communication strategies (acknowledge, give one fact, offer a role, set calm boundaries, bring backup) to respond to stigmatizing or mistaken comments about gut and mental health, and explain why each response might help or backfire.

Canvas: 420 px drawing area plus 90 px controls (iframe 512 px); responsive to about 380 px wide.

Controls: Scenario select (Aunt at dinner; Teacher and the restroom; Friend asks about missed school; Coach before a race); Restart; Choose A, Choose B, Choose C; Next.

Rules: Each scenario has two turns. The other person's second line depends on the first choice (branching). After each choice, a feedback card labels how the response might land ("Likely to land well," "Mixed: depends on the moment," or "Likely to backfire") and explains why in one or two sentences. No scores are kept.

Provenance: Section 19.9 strategies; 504 accommodations from the Crohn's & Colitis Foundation fact sheet; all characters are fictional.

Pick **Aunt at dinner** and try each first response. Notice how the aunt's next line changes depending on what Riya says: a sharp reply makes her defensive, while acknowledging her care opens a real question about Riya's medicine. Then try the **Teacher** scenario and notice how mentioning a 504 plan changes the conversation, and the **Coach** scenario, where Sam has to push back on "it's just nerves" without putting himself down.

Look closely at the "Mixed" answers. Saying nothing, or setting a firm boundary, can be the right choice for you in a particular moment; the feedback explains the trade-offs rather than grading you. After trying a few paths, write your own version of the best response in your own words.

What this model leaves out

- Real conversations don't come in three neat options, and people rarely respond the same way twice.
- Tone of voice, timing, body language, and who else is in the room matter as much as the words, and the sim can't show them.
- The sim's feedback is a teaching judgment, not research data; what lands well depends on the specific family, culture, and relationship.
- It covers only four scenarios and two turns each; real misunderstandings may take many conversations to change.
- Language matters: in many families, the most important conversations happen in a language other than English, and the sim is English only.

At the Bedside: Riya's 504 Meeting and a Family Conversation

Meet the patient (fictional)

Riya is 16, a junior at Lakeview High School, with Crohn's disease affecting the end of her small intestine and part of her colon. She takes a biologic medicine and is mostly in remission. After a mild flare in the fall, she missed several days, a teacher refused her a restroom pass during a quiz, and she started skipping lunch so she wouldn't need the bathroom in class. At home, she hasn't told her parents how anxious she's been before flares.

What the doctor checks: At her visit, Dr. Alvarez reviews Riya's symptoms, blood and stool tests, and growth, and asks how she's eating. Riya admits she's been skipping lunch. Dr. Alvarez also asks about mood and sleep using a short screening questionnaire, which shows moderate anxiety symptoms.

Connecting the signals: Skipping meals isn't a symptom of Crohn's itself; it's a way of hiding it, driven by stigma and a lack of school support. Hiding meals risks poor nutrition and makes it harder for her care team to know how she's really doing. Her anxiety may also be making her more alert to every gut sensation, as described in Chapters 8 and 11.

Diagnosis: Crohn's disease, mostly in remission, with anxiety symptoms and illness concealment linked to stigma at school.

Why it happens: Crohn's disease causes unpredictable symptoms, and stigma (from others and from herself) pushes Riya to conceal them. Concealment adds stress, and stress and anxiety can make gut symptoms feel worse, feeding the loop.

The mind-body side: Dr. Alvarez explains that hiding symptoms makes them harder to treat, and that anxiety is common and treatable in teens with IBD. She refers Riya to the clinic's psychologist for brain-gut therapy (see Chapter 18). With Riya's permission, the clinic social worker helps the family request a 504 plan.

At the 504 meeting, Riya, her mom, the school counselor, and her teachers agree on unlimited restroom access, stop-the-clock testing, a private signal to leave class, and a plan for making up work after appointments. Riya speaks for herself for part of the meeting, which she practiced beforehand.

At home, the family has a harder conversation. Her grandmother asks whether stress caused the disease; her father worries that "seeing a psychologist" will make people think something is wrong with her. The clinic's psychologist, who works with many immigrant families, explains anxiety as a common, treatable part of living with a chronic illness, and invites the grandmother to the next visit. The grandmother asks if she can keep cooking for Riya. The answer is yes.

Treatment today: Crohn's care continues with Riya's biologic medicine and regular monitoring by her gastroenterology team. Some pediatric IBD care teams include psychologists and social workers, and school accommodations like a 504 plan are a standard part of support for students with IBD. Treatment decisions are made individually with the care team.

What's new in research: In 2025, a global analysis of 522 population-based studies in *Nature* (Hracs and colleagues) mapped IBD moving through epidemiologic stages in 82 regions, which helps health systems plan for more patients from more backgrounds. **Evidence grade: Strong** for the global spread of IBD. Research on stigma and culturally responsive care for South Asian and other minority families with IBD remains limited and mostly small, so that part is **Preliminary**.

Your turn: reason through a variation

Sam's coach says Sam can't have extra restroom breaks during practice because "it's not fair to the team," and Sam doesn't have a formal plan. What would you suggest Sam and his family do?

Answer: Sam could ask his doctor for a short note explaining that IBS is a real condition and what he needs, and the family could ask the school's 504 coordinator whether accommodations can cover athletics; the Crohn's & Colitis Foundation fact sheet notes that 504 plans can include full participation in extracurricular activities for students with IBD, and the school decides eligibility for other conditions case by case. Meanwhile, Sam can explain to the coach calmly that the breaks let him stay on the team, not escape practice.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Talking about bowel symptoms is shameful, so it's better to keep them to yourself.
Reality: Bowel symptoms are normal medical information. Hiding them (illness concealment) can make conditions harder to treat, and doctors, nurses, and school staff need accurate information to help.

Myth: Getting mental health help means you're weak.
Reality: Anxiety and depression are common, especially with chronic gut conditions, and treatments like CBT work. A large review found that stigma is one of the main reasons people don't seek help, not a sign that they don't need it.

Myth: One culture's diet causes IBD, or one traditional food can cure it.
Reality: IBD is rising in many countries with very different diets, and NIDDK reports that researchers have not found specific foods that cause or worsen Crohn's symptoms. Genes and environment both contribute, and no single food or culture explains it.

Myth: Teachers aren't allowed to give students with gut conditions special treatment.
Reality: Under Section 504, a school that receives federal funding may be required to provide accommodations, such as restroom access as needed and stop-the-clock testing, to a student whose condition qualifies, usually through a 504 plan. These aren't unfair advantages; they remove barriers so students can learn.

Myth: IBD only affects white people in Western countries.
Reality: IBD is a global disease that's rising in newly industrialized countries, and studies in England found

ulcerative colitis more common in South Asian residents than in their European neighbors.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "Crohn's is a Western lifestyle disease. If you just eat the traditional food your grandparents ate, it will go away."

Grade: Hype. IBD did become common first in Western countries, and environment probably matters, which is a real part of the science. But IBD is now rising worldwide, including in countries with traditional diets, and studies of South Asian migrants suggest that genes and environment work together rather than any one diet being to blame. NIDDK reports that researchers have not found that specific foods cause or worsen Crohn's symptoms, and no trial shows a traditional diet makes Crohn's go away. A careful version: "Environment, including diet, may influence who develops IBD, but once someone has Crohn's, it needs medical treatment."

2. Predict: A school sets up an anonymous online form where students can request a restroom pass card without explaining why. Based on this chapter, predict what might happen to illness concealment among students with gut conditions.

Concealment would likely drop for some students, because the biggest stigma barrier in research is worry about disclosure. If students don't have to explain symptoms publicly, they may skip meals less and stay in class more. But some may still hide symptoms from doctors or family, so the form helps with school stigma without solving everything, and a formal 504 plan still offers stronger protection.

3. Explain: Riya's grandmother asks why, if IBD runs partly in families, second-generation South Asians in the Leicestershire study had about the same ulcerative colitis risk as first-generation migrants. Explain what migration studies can and can't tell us.

Migration studies compare groups with similar ancestry living in different environments, so they help separate genes from environment. In Leicestershire, South Asians had higher ulcerative colitis rates than Europeans living in the same place, and first- and second-generation South Asians had similar risk, which suggests both inherited factors and the shared local environment could matter. But these are older data from one county, they didn't compare with people in South Asia, and they can't identify which specific factors are responsible.

4. Apply: Sam's coach says, "Stomach again? It's just nerves. Push through." Use the five conversation moves from Section 19.9 to write a two-sentence response for Sam.

One good response: "I know you want me to race well, and nerves do make it worse, but I have IBS, which is a real gut condition my doctor is treating. Could I warm up near the restrooms on race days, and could my mom and I talk with you about a plan for meets?" It acknowledges the coach's goal, gives one clear fact, offers a concrete role, and brings in backup.

5. Read the data. In the CDC's 2025 Youth Risk Behavior Survey, students who reported persistent sadness or hopelessness were asked whether they had needed counseling or therapy but not received it ("unmet need"). Selected results:

Group (students with persistent sadness or hopelessness)	Reported unmet need for counseling or therapy
All students	28.8%
Asian American students	38.4%
Black students	33.9%
Hispanic students	29.0%
White students	27.1%

5. What does this data show, and what can't it show?

It shows that more than a quarter of struggling students said they needed counseling but didn't get it, and that unmet need was higher among Asian American and Black students than among White students. It can't show why: the survey asked only whether students needed counseling and didn't get it, not what stood in the way, so stigma is only one possible explanation alongside cost, not knowing where to go, and others. "Asian American" lumps together many different communities, including South Asian students, and the Asian estimate had a wide margin of uncertainty, so it can't describe any one community or family. A useful follow-up would survey specific communities separately and ask directly about each barrier.

Exercises

Remember

1. According to Corrigan and Watson, what are the three parts of stigma?

Answer

Stereotypes (beliefs about a group), prejudice (agreeing with the stereotype and feeling negatively), and discrimination (acting on the prejudice).

1. Name three accommodations commonly included in a 504 plan for a student with IBD.

Answer

Any three of: unlimited restroom access, stop-the-clock testing, making up missed work without penalty, tutoring after long absences, and full participation in extracurricular activities after absences.

Understand

1. Explain the difference between public stigma and self-stigma, with an example from a gut condition.

Answer

Public stigma is how other people react to a group, like classmates mocking someone for frequent bathroom trips. Self-stigma is when the person with the condition starts believing those messages, like a teen with IBS thinking, "I'm disgusting and a burden."

1. Explain why illness concealment can make a gut condition harder to treat.

Answer

If a person hides symptoms like blood in the stool, night-time bathroom trips, skipped meals, or low mood, the care team doesn't get the information it needs to adjust treatment, and schools and families can't offer support.

Apply

1. Use the Conversation Practice MicroSim to play the "Friend asks about missed school" scenario three times, choosing a different first response each time. Write down how the friend's reply changed and which path you'd actually choose, and why.
2. Using the MedlinePlus tips in Section 19.7, write a short list Riya could bring to her next appointment, including at least one "embarrassing" item and one question about a home remedy.

Analyze

1. The 2009 stigma survey included 211 adults, about 97% of whom were White. Analyze how this limits what the study tells us about teens like Riya, and design two changes that would make a future study more useful for South Asian American families.
2. Compare the Probert 1992 and 1993 Leicestershire studies with the Misra 2018 review. What does each add, and why does the pooled 2018 result not settle the question?

Evaluate

1. A wellness influencer posts: "South Asians are genetically protected from IBD, so if you get it, you must be doing something wrong." Evaluate each part of this claim using this chapter's evidence, and explain why the second sentence is harmful even apart from being false.
2. Some people argue that teens should keep their gut conditions private at school to avoid stigma. Others argue that openness reduces stigma over time. Judge which approach fits the evidence in this chapter better, and whether there's a middle path.

Create

1. Create a one-page "how to support a friend with a gut condition" guide for your school's health class, using at least three concepts from this chapter (for example, stigma, illness concealment, peer support, and school accommodation).
2. Write a new branching scenario for the Conversation Practice sim: a parent who doesn't want their teen to see a therapist. Include the parent's opening line, three possible teen responses with feedback, and a follow-up line for each.

Key Takeaways

- Stigma combines stereotypes, prejudice, and discrimination; self-stigma happens when people turn those beliefs on themselves, and mental health stigma targets mental illness and care-seeking.
- Most adults with IBD in a 2009 survey (84%) reported feeling stigmatized, and stigma was linked to worse quality of life and distress; hiding symptoms (illness concealment) makes conditions harder to treat.
- Stigma is a major barrier to mental health help, especially for young people and minority groups; in 2025, 33.3% of US high school students reported persistent sadness or hopelessness, and unmet need for counseling was higher among Asian American and Black students than among White students.
- IBD is a global disease that is rising in newly industrialized countries; it is not only "Western," and no single food or culture causes or cures it.
- Migration studies in England found ulcerative colitis (but not Crohn's) more common in South Asian residents than in Europeans, suggesting both environment and inherited factors matter; these data are older and regional.

- South Asian communities are diverse; small studies describe stigma, family dynamics, and access problems as barriers, and family care is also a major strength.
- Health literacy, preparing for doctor visits, 504 plans, and peer support are practical tools; good conversations acknowledge care, give one clear fact, offer a role, set calm boundaries, and bring backup.

You've practiced the hardest kind of science communication



Explaining your body to someone who loves you and disagrees takes real courage, and now you have facts and words to do it. In Chapter 20, the final chapter, you'll pull together every tool in this book to become your own scientist and judge any health claim you meet.

Quiz: Culture, Food, Family, and Stigma

Test your understanding of Chapter 19. Choose the best answer, then click **Show Answer** to check.

Question 1

What is self-stigma?

A. When the public reacts negatively to a group of people

B. When a school refuses to give a student accommodations

C. When a person with a condition turns negative beliefs about that condition on themselves

D. When a doctor keeps a patient's diagnosis private

Show Answer

The correct answer is **C**. Self-stigma is internalizing stigma, for example a teen with IBS thinking "I'm disgusting." Option A describes public stigma, the other form in Corrigan and Watson's framework.

Concept Tested: Self-Stigma **Bloom's Level:** Remember

Question 2

What is a 504 plan?

A. A written school plan, under Section 504 of the Rehabilitation Act of 1973, listing accommodations a student with a disability needs for equal access to education

B. A medical prescription that only a gastroenterologist can write

C. A special education plan for students with learning disabilities only

D. A plan that lowers the grades a student needs to pass

Show Answer

The correct answer is **A**. A 504 plan is developed by the school with the student and family and lists accommodations such as unlimited restroom access. Option C is wrong because 504 plans cover students with many kinds of disabilities, including chronic illnesses like IBD. IEPs, which are plans for students who need special education services, fall under a different law, the Individuals with Disabilities Education Act. Option D is wrong because accommodations remove barriers without lowering expectations.

Concept Tested: 504 Plan **Bloom's Level:** Remember

Question 3

In the 2009 survey of 211 adults with IBD, about what share reported feeling stigmatized because of their disease?

A. 10%

B. 25%

C. 50%

D. 84%

Show Answer

The correct answer is **D**. Eighty-four percent reported perceived stigma. The 10% figure (A) is a mix-up with a different number: stigma explained 10% to 22% of the variation in quality of life scores.

Concept Tested: Stigma **Bloom's Level:** Remember

Question 4

Why can illness concealment make a gut condition harder to treat?

A. Hiding symptoms makes the immune system more active.

B. If symptoms are hidden, doctors, schools, and families don't get the information they need to adjust treatment and offer support.

C. Concealment is illegal under Section 504.

D. Hiding symptoms always causes a flare within a week.

Show Answer

The correct answer is **B**. Concealment cuts off information: a doctor can't adjust treatment for symptoms they never hear about. Option A invents a direct biological effect that the chapter doesn't claim.

Concept Tested: Illness Concealment **Bloom's Level:** Understand

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Question 5

Which statement best describes the global pattern of IBD, according to the 2017 Lancet review and the 2025 Nature analysis?

A. IBD became common first in early industrialized regions and is now rising in many newly industrialized countries in Asia, Africa, and South America.

B. IBD occurs only in Western countries.

C. IBD rates are falling everywhere in the world.

D. IBD is equally common in every country and always has been.

Show Answer

The correct answer is **A**. IBD incidence has leveled off in much of North America and Europe but has been rising in newly industrialized countries since 1990. Option B is the "Western-only" myth the chapter grades as Hype.

Concept Tested: Global IBD Rise **Bloom's Level:** Understand

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Question 6

In the Leicestershire studies, first- and second-generation South Asians had similar ulcerative colitis risk, and South Asians had higher ulcerative colitis rates than Europeans living in the same county. What is the most careful interpretation?

A. South Asians are genetically protected from all forms of IBD.

B. IBD is higher in South Asians everywhere in the world.

C. Ulcerative colitis was more common among South Asians in that region and era, which suggests genes and shared environment both may matter, but the data are older and regional.

D. Traditional South Asian food causes ulcerative colitis.

Show Answer

The correct answer is **C**. The data show higher ulcerative colitis (but lower Crohn's) in one English county in the 1970s and 1980s. Option B overgeneralizes: the findings don't cover all countries or all forms of IBD, and a 2018 pooled analysis wasn't statistically significant.

Concept Tested: Migration and IBD Risk **Bloom's Level:** Understand

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Question 7

Aarav, a 15-year-old with ulcerative colitis, is preparing for a doctor's visit. He has been skipping lunch to avoid restroom trips and drinks an herbal tea his grandfather recommends. Based on the MedlinePlus tips in the chapter, what should he do?

A. Mention only his main symptom so the visit stays short.

B. Leave out the tea, since home remedies aren't medicine.

C. Wait until he has a flare before bringing anything up.

D. Write down his symptoms and questions, list everything he takes (including the tea), and tell the doctor about skipping lunch.

Show Answer

The correct answer is **D**. MedlinePlus recommends listing all medicines, herbs, and supplements and being truthful about habits and symptoms. Option B is a common mistake: home remedies are exactly the kind of information that helps keep treatment safe.

Concept Tested: Talking to Your Doctor **Bloom's Level:** Apply

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Question 8

At a family dinner, Riya's aunt says, "Just eat more ghee and stop worrying." Which reply best uses the conversation moves from Section 19.9?

A. "You don't know anything about Crohn's."

B. "I know you want me to feel better. Crohn's is an immune condition my doctor treats with medicine. Could you help me find recipes that are easy on my stomach during flares?"

C. "Okay, I'll stop my medicine and try the ghee."

D. "Crohn's comes from eating Western food, so just eat the way we used to."

Show Answer

The correct answer is **B**. It acknowledges the aunt's care, gives one clear fact, and offers her a helpful role. Option C is dangerous because no one should stop or change a medicine without their care team.

Concept Tested: Family Communication **Bloom's Level:** Apply

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Question 9

The 2009 IBD stigma survey found that people who felt more stigmatized had worse quality of life. Which is the strongest limitation of this finding for families like Riya's?

A. The study used mice instead of people.

B. The study proved that stigma causes Crohn's disease.

C. The sample was too large to analyze.

D. It was a one-time survey of mostly White adults recruited online, so it can't show cause or represent teens or South Asian families well.

Show Answer

The correct answer is **D**. A cross-sectional survey shows correlation, and a sample that is about 97% White adults says little about teens from other backgrounds. Option B reverses the logic: the study looked at stigma and outcomes, not at what causes Crohn's, and couldn't prove cause anyway.

Concept Tested: Quality of Life **Bloom's Level:** Analyze

Question 10

In the 2025 CDC survey, unmet need for counseling among students with persistent sadness was 38.4% for Asian American students and 27.1% for White students. Which conclusion is best supported?

A. Some groups may face extra barriers to care, but the data can't show which barriers, and "Asian American" combines many different communities.

B. South Asian families do not believe in therapy.

C. Asian American students have more depression than any other group.

D. The difference proves that stigma is the only barrier.

Show Answer

The correct answer is **A**. The survey asked whether students needed counseling and didn't get it, not why, and it used a broad "Asian" category with a wide margin of uncertainty. Option B turns a group statistic into a stereotype about families, which the data can't support.

Concept Tested: Help-Seeking Barriers **Bloom's Level:** Analyze

Chapter 20: Be Your Own Scientist: Reading Health Claims

Summary

This final chapter turns the Hype Meter and the six claim questions into a complete method you can use on any health claim, gut-brain or not. You will learn how scientists rank different kinds of evidence, why most mouse results don't carry over to people, and what peer review, preprints, and preregistration can and can't promise. Then you'll work through the numbers that headlines love to bend: p-values, "statistically significant," and relative versus absolute risk. You will also learn how supplement marketing is regulated, how to read an abstract, and how to write about science honestly. The chapter ends with a template for your own student research project.

Concepts Covered

1. Hierarchy of Evidence
2. Mouse-to-Human Translation
3. Peer Review
4. Preprint
5. Conflict of Interest
6. Preregistration
7. Statistical Significance
8. Absolute vs Relative Risk
9. Health Claim Marketing
10. Structure-Function Claim
11. Reading an Abstract
12. Claim-Checking Method
13. Science Communication
14. Student Research Project

Prerequisites

- Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading) (the Hype Meter and the six questions)
- Chapter 16: Probiotics, Prebiotics, and "Psychobiotics"
- Chapter 17: Medicine for the Gut-Brain Axis
- Helpful: any of Chapters 2 to 19, since the claims in this chapter come from all of them

Your turn to be the scientist



For nineteen chapters, I've been grading claims for you. This chapter hands you the grading pen. The gut-brain axis will keep producing exciting headlines long after you finish this book, and the skills here will let you sort the real advances from the sales pitches on your own. Let's check the evidence, one last time, together.

20.1 Three Posts in One Scroll

It's Tuesday night, and Sam should be studying for a chemistry test. Instead, he's scrolling. The first post is from his older cousin: a smiling influencer holding a bottle of gummies. "My anxiety is GONE," the caption says. "These probiotics rewired my gut-brain axis. Backed by science!" The second post is an ad for a small device you clip to your ear. "Activate your vagus nerve. Melt stress in minutes." The third is a news story Riya sent him: "New pill puts Crohn's disease into remission, study finds."

Sam has IBS and test anxiety, so the first two posts are aimed right at him. Riya has Crohn's disease, so the third one could matter for her. All three use the language of science. All three sound hopeful. Which one deserves their trust? (Sam and Riya are fictional students who appear throughout this book.)

The next day at science club, Riya and Sam pitch a project: a claim-checking guide any student could use on posts like these. Their advisor agrees, on one condition: the guide must explain *why* a claim earns its grade. That project is the thread of this chapter.

20.2 Thinking Like a Detective

Before any technical terms, picture a detective at a crime scene. Several witnesses tell their stories. One saw the whole thing up close. One heard about it from a friend. One is the suspect's business partner. A good detective doesn't believe everyone equally, and doesn't dismiss everyone either. She asks: How close was this witness to what happened? Do the stories agree? Does anyone have a reason to bend the truth?

Reading a health claim works the same way. The evidence is the witnesses: some strong (a large trial in people), some weak (a single testimonial), some with a motive (a company studying its own product). Your job isn't to be cynical. It's to be **calibrated**: trust strong evidence, doubt weak evidence, and know the difference.

You already have two tools from Chapter 1, Section 1.12: the four Hype Meter grades and the six questions (refresher on the Hype Meter page). This chapter makes those questions sharper, then combines everything into a step-by-step method in Section 20.12.

20.3 Not All Evidence Is Equal: The Hierarchy of Evidence

Does a new pill help IBS? Your aunt took it and felt better. A lab paper shows it changes gut cells in a dish. A study of thousands of people found pill-takers had fewer symptoms. A trial randomly assigned people to the pill or a fake pill. All four are "evidence." They aren't equally convincing.

The **hierarchy of evidence** is the idea that different kinds of studies give different levels of confidence about cause and effect, often drawn as a pyramid with the weakest kinds at the bottom and the strongest at the top. Here is a common version, from bottom to top:

Level (weakest to strongest)	What it is	What it can show	Main weakness
Testimonials, anecdotes, expert opinion	One person's story or one expert's view	That something is possible or worth studying	No comparison group; memory and hope bias the story
Lab and animal studies	Cells in dishes, mice, rats	How something *might* work (mechanism)	Often doesn't carry over to people
Case reports and case series	Doctors describe one patient or a handful	Rare events, new patterns	Tiny numbers, no comparison
Observational studies	Researchers watch large groups without changing anything	Links (correlations) in real people	Can't rule out reverse causation or hidden third factors
Randomized controlled trials (RCTs)	People are randomly assigned to a treatment or a comparison, often a placebo	Whether the treatment *causes* a change	Expensive, often short, may exclude many kinds of patients
Systematic reviews and meta-analyses	Researchers gather all the good studies on a question and combine them	The overall picture across many studies	Only as good as the studies inside them

The National Center for Complementary and Integrative Health (NCCIH), part of the US National Institutes of Health, describes a similar ladder from basic research to clinical trials, which give the clearest information

about whether a treatment works and is safe in people. When many studies reach the same conclusion, NCCIH notes, the result is more reliable.

Why are randomized trials so powerful? Randomization is like shuffling a deck before dealing two hands. People who choose a pill might already be healthier or more motivated; a coin flip spreads those differences evenly, so the main remaining difference is the treatment. A placebo (a look-alike fake treatment) and "blinding" (people don't know their group) remove the power of expectation, which matters a lot for pain, mood, and gut symptoms.

The pyramid is a starting point, not a law. In 2016, Murad and colleagues proposed a "new evidence pyramid" in which systematic reviews act like a lens for viewing the other studies, because a review of ten tiny, biased trials is still weak. And some questions can't be answered by trials at all (you can't assign teens to smoke for 20 years), so for some harms, large observational studies are the best evidence possible. Roughly, Strong grades rest on trials or many consistent human studies, and Hype grades rest on testimonials or a single mouse study dressed up as proof.

20.4 The Mouse Problem: Mouse-to-Human Translation

Mice are amazing research partners: scientists can control their diet, genes, and even their microbes. Germ-free mice, mice given human gut bacteria, and mice with a cut vagus nerve taught us how gut-brain signaling *can* work.

But a mouse is not a small person. **Mouse-to-human translation** is the process of testing whether a finding in mice (or other animals) holds true in people, and the frequent failure of animal results to carry over. Here is what the research on translation itself shows:

- **Even famous animal studies usually don't translate.** In 2006, Daniel Hackam and Donald Redelmeier looked at 76 highly cited animal studies. In a 2007 article, Hackam summarized the result: only about one in three were later confirmed in human randomized trials.
- **Mouse biology can differ in basic ways.** A 2013 study by Seok and colleagues found that mouse gene responses to serious inflammation (burns, trauma, a bacterial toxin) barely matched human ones, close to chance. That was about inflammation models only, and a 2014 reanalysis of the same data by Takao and Miyakawa, using a different way of choosing which genes to compare, reached the opposite conclusion. So the finding is debated. It doesn't mean mouse studies never work, only that you can't assume they will.
- **Microbiome mouse studies may be too good to be true.** In 2020, Walter and colleagues reviewed studies that moved gut microbes from sick people into germ-free rodents. In 95% of them (36 of 38), the disease trait supposedly "transferred" along with the microbes. The authors called that success rate implausible and warned that it overstates the microbiome's role in human disease.

The clearest example in this book comes from Chapter 16. In 2011, Bravo and colleagues gave mice a probiotic strain called *Lactobacillus rhamnosus* JB-1. The mice showed less anxiety-like behavior and a lower stress-hormone response, and cutting the vagus nerve blocked the effect. It was exciting, careful work.

Then, in 2017, Kelly and colleagues gave the same strain to 29 healthy men in an 8-week randomized, placebo-controlled trial. It did nothing measurable for stress, mood, anxiety, sleep, memory, inflammation, or brain-wave patterns. The paper's title began, "Lost in translation?"

A mouse result is a question, not an answer



When I see "a study found" followed by something about mice, I mentally rewrite it as "scientists have a new question to test in people." The JB-1 story shows why: the mouse result was real, and it still didn't hold up in humans.

The Kelly trial didn't prove JB-1 is useless for everyone: it was small and tested healthy men, not people with anxiety disorders. That's how to describe a negative result honestly.

Hype Meter: "This probiotic is proven to lower stress (it worked in a study!)"

Strong	Moderate	Preliminary	**Hype**

Verdict: Hype. The best-known "stress probiotic" study, Bravo 2011, was done in mice. When the same strain was tested in 29 healthy men for 8 weeks with a placebo comparison (Kelly 2017), it had no measurable effect on stress, mood, or thinking. Probiotic effects also depend on the exact strain, so a result for one strain doesn't transfer to others. **What would change the grade:** Several large, placebo-controlled trials of a specific strain in people with stress or anxiety problems, by independent teams, showing a consistent benefit. That could move the claim for that strain to Preliminary or Moderate.

20.5 How Research Gets Published: Preprints and Peer Review

When scientists finish a study, they write it up as a paper. What happens next affects how much you should trust it.

Many researchers first post their paper as a **preprint**: a complete scientific paper shared publicly online before it has been checked by peer review. Preprint servers such as medRxiv (for health research) let anyone read new findings within days. But medRxiv's own website warns that preprints are preliminary reports that haven't been certified by peer review, shouldn't be used to guide health decisions, and shouldn't be reported in news media as established information.

News stories sometimes skip that warning. If a headline cites a preprint, treat the finding as Preliminary at best until it is reviewed and confirmed.

Peer review is the process in which a journal sends a submitted paper to independent experts in the same field, who check its methods, reasoning, and conclusions and recommend whether it should be published,

revised, or rejected. Think of a building inspector: good at catching cracked foundations, but unable to test every wire behind the walls.

Here's what peer review does and doesn't do:

Peer review usually checks	Peer review usually can't check
Whether the study design fits the question	Whether the raw data are accurate (reviewers rarely see them)
Whether the conclusions follow from the results	Whether the result will repeat in another lab
Whether important limits are mentioned	Whether all the analyses tried were reported
Whether the paper explains its methods clearly	Whether the finding applies to people unlike those studied

Published doesn't mean proven



"Published in a peer-reviewed journal" means experts thought a study was worth sharing, not that its conclusion is true. The mouse JB-1 study and the human JB-1 trial were both peer reviewed, and they disagreed. Science moves forward when many studies line up, not when one passes inspection.

20.6 Calling Your Shot: Preregistration

Picture a basketball player who shoots from half court, sinks it, and then announces, "I meant to bank it off the glass." You'd be more impressed if she called the shot before she threw.

Research has the same problem. If scientists measure 20 different outcomes and then report only the one that came out well, the "finding" may be pure luck. Nosek and colleagues, in a 2018 paper, describe this as confusing *postdiction* (explaining results after you see them) with *prediction* (testing an idea you stated in advance). Even honest researchers fall into it, because hindsight makes any pattern look like what you expected.

Preregistration means publicly recording a study's question, main outcome, and analysis plan before collecting or looking at the results, so readers can check that the researchers tested what they said they would. For clinical trials, public registries such as ClinicalTrials.gov hold these plans. Each registered trial gets an ID number that starts with "NCT." The International Committee of Medical Journal Editors (ICMJE), whose

rules many major medical journals follow, requires trials to be registered at or before the time the first patient enrolls, as a condition for considering the paper.

As a reader, look for the registration number, then compare the registered main outcome with the one the paper headlines. If the registry planned pain scores but the paper trumpets sleep quality, ask why. Preregistration doesn't make a study correct, and exploring surprises is normal science; it just keeps planned tests and surprise findings clearly labeled.

20.7 What "Statistically Significant" Really Means

Headlines love the phrase "statistically significant." It sounds like "important." It doesn't mean that.

Flip a fair coin 10 times and you might get 7 heads by luck. Getting 700 heads in 1,000 flips would be shocking. Statistics asks: if the treatment did nothing, how surprising would our results be?

Statistical significance is a label researchers give a result when it would be unlikely to occur by chance alone if there were truly no effect, usually judged by a p-value below a cutoff such as 0.05. The **p-value** is a number between 0 and 1. A small p-value means "data like these would be surprising if the treatment did nothing." It does not tell you how big or how useful the effect is.

In 2016, the American Statistical Association (ASA), the largest organization of statisticians, released a statement with six principles about p-values because they are so often misused. Two of the principles are especially useful for reading headlines:

- A p-value, or statistical significance, does not measure the size of an effect or the importance of a result.
- Scientific conclusions shouldn't be based only on whether a p-value passes a specific cutoff.

In a huge study, a tiny, meaningless difference can be "significant," while a small study can miss a real effect. So after "significant," always ask: **How big was the difference? Would a person notice it?**

Stats feel slippery at first



If p-values make your head spin, you're in good company; professional scientists argue about them too. For reading headlines, you only need one habit: whenever you see "significant," look for the actual numbers and ask how big the difference was.

Small studies cause a second problem. In 2013, Button and colleagues showed that the average neuroscience study has very low statistical power, meaning it's too small to reliably detect real effects. Low power has a sneaky side effect: when a small study does find something, the effect it reports is more likely to be exaggerated or false.

In 2005, John Ioannidis published a famous paper arguing that research findings are less likely to be true when studies are small, effects are small, designs are flexible, and there are financial interests. That paper

was a modeling argument, not a count of false studies, so it doesn't mean "most research is wrong." It's a list of warning signs, and the gut-brain field has many of them.

Watch for one more trick: **picking the good number.** In Chapter 16, you met a 2024 review of 12 probiotic trials with 707 people. Probiotics showed a significant benefit on one depression questionnaire (the Beck Depression Inventory) but not on three others. A headline could truthfully say "probiotics significantly reduced depression scores" while leaving out the three scales that showed no significant difference. That's why the book grades "probiotics treat depression" as Preliminary.

20.8 Absolute vs Relative Risk: Same Data, Different Headlines

Suppose a store advertises "50% off!" That sounds huge, until you learn the item was a 2-dollar pack of gum. The percentage is real, but the actual savings are a dollar. Risk numbers work the same way.

Absolute vs relative risk is the difference between two ways of describing how much a treatment changes the chance of an outcome. **Absolute risk** is the actual chance of the outcome in a group (for example, 12 out of 100 people). The absolute risk difference is the simple subtraction between groups, in percentage points. **Relative risk** compares the two groups as a ratio, so a change can sound large even when the actual numbers are small.

Let's use a real example from Chapter 17. In the ECOSPOR III trial, published in 2022 in the *New England Journal of Medicine*, 182 adults who had recurrent *C. difficile* (C. diff) infections took either an oral microbiome treatment called SER-109 or a placebo after their antibiotics. Within 8 weeks, the infection came back in 12% of the SER-109 group and 40% of the placebo group (12.4% vs 39.8% before rounding). The FDA approved SER-109 as Vowst on April 26, 2023, to prevent C. diff from coming back in adults 18 and older after antibiotic treatment for recurrent infection.

Here are three accurate ways to describe the same result:

Way of describing it	Calculation	How it sounds
Absolute risk difference	$40\% - 12\% = 28$ percentage points	"28 fewer people out of every 100 had the infection come back"
Relative risk	$12\% \div 40\% \approx 0.3$ (the paper reports 0.32)	"Recurrence risk was about one-third as high"
Relative risk reduction	$1 - 0.32 = 0.68$	"68% lower risk of recurrence"

Another useful number is the **number needed to treat** (NNT): about how many people need the treatment for one extra person to benefit. It's 1 divided by the absolute risk difference:

$$\text{NNT} = \frac{1}{0.40 - 0.12} = \frac{1}{0.28} \approx 3.6$$

So about 4 people would need treatment to prevent one recurrence: a strong effect by either measure.

Relative risk can also mislead. **Practice data (made up for this exercise):** if a rare side effect hits 1 in 10,000 people without a supplement and 2 in 10,000 with it, "doubles your risk!" is technically true, but the absolute difference is 1 extra case per 10,000 people. Only together do the two numbers tell the whole story.

Always ask: out of how many?



When a headline says "cuts risk by half" or "doubles your risk," hunt for the starting number. Half of 40% is a big deal; half of 0.02% might not change anyone's life.

Hype Meter: "An FDA-approved microbiome pill helps stop C. diff from coming back"

Strong	Moderate	Preliminary	Hype

Verdict: Strong. A phase 3 (large, late-stage; see Chapter 17), double-blind, placebo-controlled trial of 182 adults found recurrence of 12% with the treatment versus 40% with placebo at 8 weeks, and the FDA approved it as Vowst in 2023. The approval covers one specific use: preventing recurrence in adults 18 and older after antibiotic treatment for recurrent C. diff. **What would change the grade:** Longer follow-up showing safety problems, or failed replication. Note that the Strong grade does not extend to other uses, such as anxiety, autism, or weight; those would need their own trials.

20.9 Follow the Money: Conflict of Interest

Imagine a restaurant review written by the owner. It might be accurate; you'd still want a second opinion. A **conflict of interest** is a situation in which a researcher, author, or organization has financial or personal ties (such as funding, a job, stock, or a patent) that could influence, or seem to influence, how research is designed, interpreted, or reported. Good journals require authors to disclose these ties in a funding statement and a conflict-of-interest statement, usually near the end of the paper.

Does funding actually change results? A 2017 Cochrane review by Lundh and colleagues combined 75 papers that compared drug and device studies by who paid for them. Studies sponsored by the company that made the product more often reported favorable results (relative risk 1.27) and more often reached favorable conclusions (relative risk 1.34) than studies with other funding. The usual quality checks for bias didn't explain the difference. The authors concluded that industry sponsorship itself is linked to more favorable results.

That doesn't make industry-funded research fake. Most new medicines are tested in trials paid for by their makers, because trials are expensive. A conflict of interest is a reason to look harder, not to throw a study away. Ask: Was it preregistered? Blinded? Do independent studies agree?

Here is the ECOSPOR III trial run through the six questions:

How to read a gut-brain claim: the ECOSPOR III microbiome pill trial

Question	This study
Mouse or human?	Human. 182 adults who had had at least three episodes of C. diff infection (counting the current one), whose symptoms had cleared after standard antibiotics.
Correlation or cause?	Cause. It was a randomized, double-blind, placebo-controlled phase 3 trial, the strongest single-study design for testing a treatment.
How many?	182 enrolled (281 were screened). Large enough to show a big difference, but rare side effects need larger numbers to detect.
How long?	The main outcome was recurrence within 8 weeks. It doesn't show how people did years later.
Who paid for it?	Seres Therapeutics, the company that developed the treatment. Many of the authors worked for Seres. The trial was preregistered (ClinicalTrials.gov NCT03183128, submitted in June 2017, before it started in July 2017).
Is something being sold?	Yes. The treatment is now sold as Vowst, approved by the FDA in 2023 for one specific use.

The verdict: a strong trial with a clear, large effect, which the FDA reviewed before approving the product. Company funding and a product for sale are facts a careful reader notes. Here they're balanced by randomization, blinding, preregistration, and an independent regulatory review. The result applies to adults with recurrent C. diff, not to anyone else.

20.10 Selling the Gut: Health Claim Marketing and Structure-Function Claims

Now back to Sam's cousin and those gummies. Why can a supplement company say "supports a healthy gut-brain connection" without the kind of trial Vowst needed?

Health claim marketing is the use of health-related promises, such as "boosts immunity," "clinically proven," or "reduces stress," to sell products. It includes labels, ads, websites, and influencer posts. It's regulated, but less strictly than many people assume, and the rules differ for drugs, foods, and supplements.

In the US, most probiotics are sold as dietary supplements. Under a 1994 law called the Dietary Supplement Health and Education Act (DSHEA), supplements don't need FDA approval before they're sold. Instead of proving that they treat a disease, supplement labels can make a different kind of claim.

A **structure-function claim** is a statement that a supplement or food supports the normal structure or function of the body (for example, "calcium builds strong bones" or "fiber maintains bowel regularity") without claiming to diagnose, treat, cure, or prevent a disease. According to the FDA, these claims aren't preapproved. The maker must have evidence that the claim is truthful and not misleading and must notify the FDA no later than 30 days after first marketing it. A supplement label with such a claim must include a disclaimer saying the FDA hasn't evaluated the claim and that the product isn't intended to "diagnose, treat, cure or prevent any disease." Only a drug can legally make that kind of disease claim.

Compare these pairs:

Structure-function claim (allowed on a supplement with the disclaimer)	**Disease claim (needs drug-level approval)**
"Supports digestive comfort"	"Treats IBS"
"Supports a balanced mood"	"Relieves depression"
"Promotes a healthy gut-brain connection"	"Cures anxiety"
"Helps maintain healthy immune function"	"Prevents infections"

The left column sounds almost the same as the right but promises less, and that gap is where a lot of marketing lives. Vague words like "supports" plus the small-print disclaimer mean the product hasn't been shown to treat a disease.

Advertising has its own referee. In December 2022, the US Federal Trade Commission (FTC) published its Health Products Compliance Guidance, replacing its 1998 supplement advertising guide. Health claims in ads generally need "competent and reliable scientific evidence," usually randomized trials in people; animal and lab studies aren't enough alone, and testimonials never count as proof. So "My anxiety is GONE!" in a paid post isn't evidence, even if the person truly feels better.

For families

Parents and grandparents often share health posts out of love. If a relative sends a gut-health product, thank them for caring and suggest checking it together with the six questions, without mocking the post or the person; the difference between a structure-function claim and a disease claim isn't obvious to anyone. For any supplement, the safest next step is to bring the label to the teen's doctor or pharmacist, especially if the teen takes other medicines.

20.11 Reading an Abstract

News stories are written to be read. Scientific papers are written to be checked. The bridge between them is the abstract.

Reading an abstract is the skill of extracting a study's question, methods, main results, and limits from the short summary at the top of a scientific paper, and comparing what it actually found with how others describe it. NCCIH advises going to the original source, the journal article, instead of trusting a news story alone. Most papers follow the same plan: abstract, introduction, methods, results, discussion, and references. Abstracts are free on PubMed (pubmed.ncbi.nlm.nih.gov) even when the full paper costs money.

Many medical abstracts use labeled sections. Here's what to pull from each:

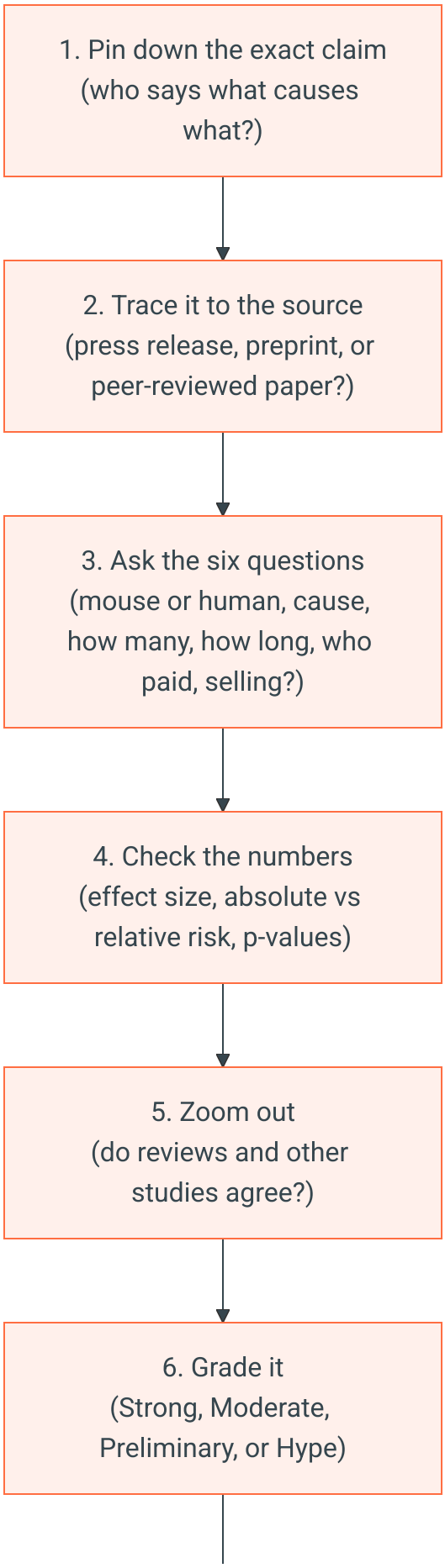
Abstract section	What to look for	Red flags
Background	What question the study asks	A question much narrower than the headline
Methods	Mouse or human; how many; randomized or not; placebo or not; how long; main outcome	Animals, tiny numbers, no comparison group
Results	The actual numbers in each group, not just "significant"	Only p-values, no group numbers; a different outcome than the one planned
Conclusions	What the authors themselves claim	Words like "may" and "suggests" that become "proves" in the news
Funding and registration	Who paid; the trial registry number	No registration for a trial; undisclosed company ties

Let's practice on the ECOSPOR III abstract (PubMed ID 35045228). Its methods section says it was a phase 3, double-blind, randomized, placebo-controlled trial in patients who'd had three or more C. diff episodes. Its results give the group numbers (12% vs 40%) and the relative risk (0.32). Its conclusion is careful: the treatment was better than placebo at reducing recurrence in patients whose symptoms had resolved after antibiotics. And its last line lists the funder and registration number. In one paragraph, you can answer all six questions.

A **press release** is different: an announcement written by a company's or university's communications staff to get coverage. It isn't peer reviewed and often leads with the most exciting number. When a news story is based on a press release, find the abstract before you believe the headline.

20.12 Putting It Together: The Claim-Checking Method

You now have all the pieces. The **claim-checking method** is this book's step-by-step process for judging any health claim: state the exact claim, trace it to its original source, ask the six questions, check the numbers and the money, weigh it against the wider body of evidence, and assign a Hype Meter grade with a careful rewrite.


1. Pin down the exact claim (who says what causes what?)
2. Trace it to the source (press release, preprint, or peer-reviewed paper?)
3. Ask the six questions (mouse or human, cause, how many, how long, who paid, selling?)
4. Check the numbers (effect size, absolute vs relative risk, p-values)
5. Zoom out (do reviews and other studies agree?)
6. Grade it (Strong, Moderate, Preliminary, or Hype)

7. Rewrite it honestly (what a careful version would say)

Three tips matter most. In step 1, "probiotics are good for your brain" is too fuzzy to grade; grade the claim *as stated*, in testable words. In step 5, remember that one study rarely settles anything: NCCIH's health news checklist asks whether this is the first time a study has reported these results, so look for a systematic review or clinical guideline. And in step 7, the rewrite should fit the grade you gave, even if it's "scientists are just starting to test this in people."

Here are the book's grades for some of the most common claims from earlier chapters. Use them to check your calibration:

Claim	Book's grade	Key reason	Chapter
"More than 90% of your body's serotonin is made in your gut."	Strong	Consistent human and animal evidence	5
"Implanted vagus nerve stimulation is FDA approved for treatment-resistant depression."	Strong	Approved in 2005 as an add-on for adults after 4 or more failed treatments; the approval is the Strong fact, while evidence of benefit is Moderate	17
"Gut-directed hypnotherapy can ease IBS symptoms."	Moderate	A 2020 analysis of 41 trials of psychological therapies found benefit, but many had a high risk of bias	18
"Poor sleep is linked to later Crohn's flares."	Preliminary	One large patient study found a link; it needs repeating, and cause is not proven	18
"Probiotics treat depression."	Preliminary	Mixed results: one questionnaire out of four improved in a 2024 review	16
"Vagus nerve stimulation can calm Crohn's disease."	Preliminary	Only small open-label studies (7 and 16 patients) with no comparison group; not approved for Crohn's	17
"70% of your immune system lives in your gut."	Hype	About 70% of antibody-making plasma cells, but only about 3% of all immune cells	4

Claim	Book's grade	Key reason	Chapter
"Leaky gut causes autism."	Hype	No human evidence of cause; autism is a neurodevelopmental difference, not a gut disease	13

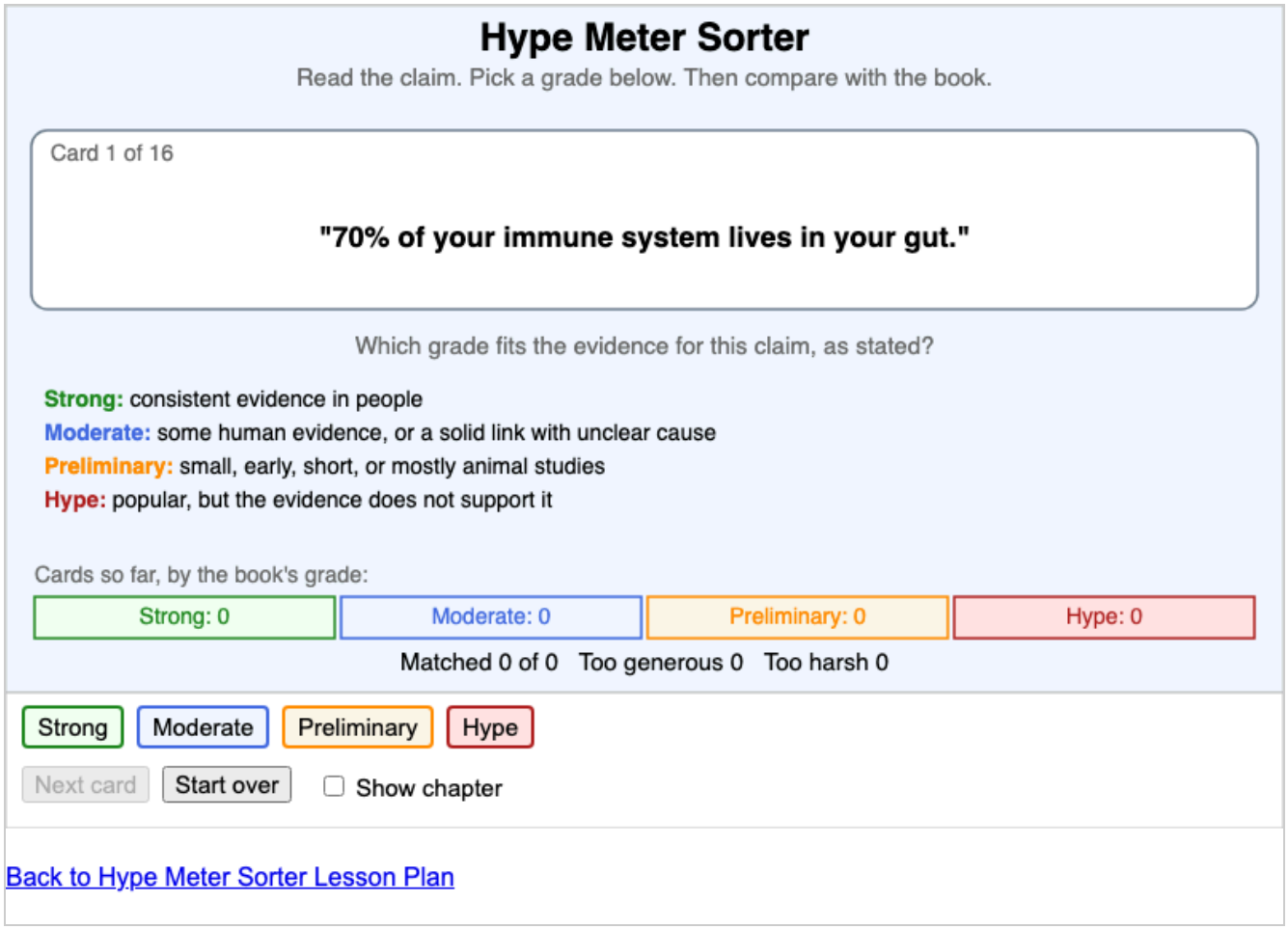
Hype Meter: "A new study found that..."

Strong | Moderate | **Preliminary** | Hype

Verdict: Preliminary, until you check. A single new study can be anything from a mouse experiment to a large trial, so the honest starting grade is "it depends." Most first-time findings, especially in mice or small groups, are Preliminary, and NCCIH reminds readers that one study rarely proves anything. A large, preregistered, randomized trial in people can earn more, especially when it agrees with earlier work. **What would change the grade:** Tracing the headline to the study. Human, randomized, large, preregistered, and replicated moves it up. Mouse-only, tiny, unregistered, or company-funded with no independent check keeps it at Preliminary or pushes it toward Hype if the headline overstates it.

The MicroSim below lets you practice the grading step on 16 real claims from across the book.

Diagram: Hype Meter Sorter



Interactive simulation: https://aaryavvatts-lab.github.io/gut-brain-textbook/sims/ch20-hype-meter-sorter/main.html

Open the Hype Meter Sorter fullscreen

MicroSim specification: Hype Meter Sorter

Type: microsim **sim-id:** ch20-hype-meter-sorter
Library: p5.js
Status: Implemented
Bloom Level: Evaluate
Bloom Verb: judge
Learning Objective: The learner will judge popular gut-brain claims by assigning a Hype Meter grade (Strong, Moderate, Preliminary, or Hype) based on the evidence behind each claim as stated, and will check whether their misses lean too generous or too harsh.

Canvas: 430 px drawing area plus 85 px controls (iframe 517 px); responsive to about 380 px wide.

Controls: Four grade buttons (Strong, Moderate, Preliminary, Hype); Next card; Start over (reshuffles); Show chapter checkbox (hint).

Cards: 16 claims from Chapters 1, 4, 5, 7, 11, 13 to 18, spread across all four grades. Each card stores the book's grade, the source chapter, and a one-sentence reason.

Feedback: After each choice, a colored panel shows the book's grade, whether the learner's grade matched, was too generous (closer to Strong), or too harsh, and the reason. A tally counts cards by the book's grade, matches, and misses in each direction. A summary screen appears after all 16 cards.

Provenance: Grades and numbers match CLAUDE.md canonical values and the verified dossiers for Chapters 1 to 19 (for example Sender 2023, Rahmannia 2024, Black 2020, Feuerstadt 2022, FDA PMA P970003/S050). Not animated, so it has no Start/Pause button.

Sort all 16 cards without the chapter hint first, running the six questions in your head. When you miss, decide which evidence feature you overlooked. Pay attention to the two vagus nerve cards and the two serotonin cards: in each pair, the topic is the same but the grades differ completely, because the claims say different things.

At the end, check your "too generous" and "too harsh" counts. Claims are written to sound convincing, so it's easy to lean generous; some people overcorrect and call everything Hype. The goal is calibration.

What this model leaves out

- Real evidence is a sliding scale, not four boxes. Some claims sit on the line between two grades, and careful experts can disagree.
- Each card gives one sentence of reasoning; a real grade weighs many studies, their quality, and their size.
- The sim grades claims as of October 2026. New studies can move a grade up or down, which is why the book logs corrections.
- The sim doesn't test the hardest step in real life: finding and reading the original study behind a post.
- A grade describes evidence for a claim in general, not what's right for any one person. That's a decision for a person and their doctor.

20.13 Science Communication: Saying It Right

Once you can grade a claim, you can do something even more useful: explain it to others. **Science communication** is the practice of explaining scientific findings to non-experts accurately, clearly, and with the right level of certainty, without hiding uncertainty or exaggerating results.

It's not about sounding cautious all the time; it's about matching your words to your evidence. Here's a word ladder:

Evidence	Words that fit	Words to avoid
Strong	"shows," "causes," "reduces," "is approved for (specific use)"	Adding uses that weren't tested
Moderate	"is linked to," "probably helps," "several studies suggest"	"proves," "cures"
Preliminary	"early studies suggest," "in mice," "a small study found," "scientists are testing"	"shows," "breakthrough," "game changer"
Hype	"there's no good evidence that," "this stretches a real finding"	Repeating the claim without the correction

Riya and Sam used this ladder for their club project. Here's how they rewrote Sam's three posts from Section 20.1:

- **The gummy post** became: "Some probiotic trials found small mood improvements, but results are mixed, and testimonials aren't evidence. If anxiety gets in your way, a doctor or counselor can help you find

treatments with strong evidence."

- **The ear-clip ad** became: "Implanted vagus nerve stimulators are FDA approved for a few specific conditions. Consumer ear devices for stress haven't been shown to work." (see Chapter 17).
- **The Crohn's headline** waited until they found the actual study (see At the Bedside below).

One more principle: **correct without shaming.** People share hype out of hope. "Here's what the studies found" works better than "That's fake."

20.14 Your Turn: A Student Research Project

The final skill is producing evidence summaries yourself. A **student research project** is a structured investigation in which a student picks one health claim, finds and evaluates the original evidence, assigns a Hype Meter grade, and explains the result in plain language for a real audience. Riya and Sam's club guide used the template below, and you can too. It works for a class assignment, a science fair, or a club presentation.

Student research project template

1. **The claim.** Copy it exactly, with where and when you found it, who made it, and whether they sell anything.
2. **The question.** Restate it as "In [which people], does [what] cause [which outcome], compared with [what]?"
3. **Sources.** At least three: the original study (or a note that none exists), a systematic review or guideline if one exists, and a plain-language source such as NIH, NCCIH, CDC, FDA, or MedlinePlus.
4. **Six-question table.** Fill in a claim box for the main study.
5. **The numbers.** Report group results, convert relative to absolute risk if you can, and note whether "significant" was also big.
6. **The grade.** Strong, Moderate, Preliminary, or Hype, with two or three sentences of reasoning and what study would change it.
7. **Plain-language summary.** 100 to 150 words for a 9th grader, using the word ladder in Section 20.13.
8. **Limits and safety.** Say what the project can't tell anyone, and include "talk to your doctor before starting, stopping, or changing any medicine, diet, or supplement."
9. **References.** Every source, with a working link you opened yourself.

If you're going through this

If you live with Crohn's, colitis, IBS, celiac disease, or another condition, you may get flooded with miracle-cure posts, sometimes from people who love you. It's okay to feel hopeful when you read them, and it's okay to feel tired of them. You don't have to evaluate every post alone. Bring the ones that interest you to your care team; many doctors appreciate patients who ask "What's the evidence for this?" And please don't start, stop, or change a medicine, diet, or supplement on your own because of a post. Make that call with your doctor.

At the Bedside: Reading the Headline Together

Meet the patient (fictional)

Riya, 16, has had Crohn's disease since 14 and is mostly in remission on a biologic medicine. Her grandmother texts her a news story: "New pill puts Crohn's into remission, study finds." Riya wants to know if she should switch from injections to the pill. She brings the article to her next visit with Dr. Alvarez, her pediatric gastroenterologist.

What the doctor checks: Dr. Alvarez first checks on Riya herself: how she's feeling, any new symptoms, how she's handling school, and her recent lab results. Then she asks to see the article. Together they trace it: the news story was based on a company press release, which linked to a conference presentation. A trial registration number led them to the study's entry on ClinicalTrials.gov. (The drug in this case is fictional; we'll call it "Drug X.")

Connecting the signals: They compare the documents side by side. The results hadn't been published in a peer-reviewed journal yet, and the registry told a narrower story than the headline:

What the press release said	What the trial record showed
"Puts Crohn's into remission"	Remission on a symptom score at 12 weeks; colonoscopy results not yet reported
"Breakthrough pill"	A phase 3 trial; not yet reviewed by the FDA
No mention of age	Adults 18 and older only
"Patients"	Adults whose disease had not responded to at least one biologic

Diagnosis: Crohn's disease, in remission on her current treatment. The new question isn't a medical diagnosis; it's a case of hopeful headline meets incomplete evidence.

Why it happens: Press releases are written to attract attention, and news stories often repeat them. This is the claim-checking method in action: trace the source, check who was studied, compare planned and reported outcomes, and notice what isn't known yet (long-term safety, effects in teens, peer review, FDA review).

The mind-body side: Riya admits she felt a rush of hope, then a crash of worry that she was "missing out" on something better. Dr. Alvarez tells her that hope is good, and that checking keeps hope honest. Living with a chronic illness means hearing about many "breakthroughs," and the swing between excitement and disappointment can be exhausting. She suggests Riya keep a list of questions about new treatments for visits, and reminds her that the clinic's psychologist is available if worry starts to affect sleep, school, or mood.

Treatment today: Riya's current biologic is working, so the plan stays the same. Crohn's treatment for teens is chosen by the care team based on disease location, severity, past response, growth, and safety, and a drug tested only in adults needs more information before it's considered for a teen. They agree to revisit the question if Drug X is approved and studied in younger patients.

What's new in research: New Crohn's medicines do reach patients after this kind of testing. For example, in January 2025, the FDA approved mirikizumab for adults with moderately to severely active Crohn's disease, based on results from the phase 3 VIVID-1 trial at one year. **Evidence grade: Strong** for its approved use in adults, because the approval rested on large randomized trials. That grade applies to adults with moderate to severe Crohn's, not to every person with Crohn's, and whether it fits any one patient is a decision for their care team.

Your turn: reason through a variation

A month later, Riya's cousin forwards a different headline: "Gut bacteria trigger Crohn's, scientists discover." The underlying paper is a mouse study in which microbes from people with Crohn's caused gut inflammation in germ-free mice. How should Riya grade the headline?

Answer: The study is in mice, so the honest grade for "gut bacteria trigger Crohn's in people" is Preliminary at best, and the headline's certain tone ("discover") pushes it toward Hype. Walter and colleagues (2020) found that 95% of studies moving human microbes into germ-free rodents reported that disease traits transferred, a rate they called implausible. A careful rewrite: "In a mouse study, microbes from people with Crohn's caused gut inflammation. Scientists still need to learn whether microbes help start Crohn's in humans, or change because of it."

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: If a study passed peer review, its conclusion is true.
Reality: Peer review checks whether a study's methods and reasoning look sound, but reviewers rarely see the raw data or repeat the experiment. Peer-reviewed studies can still be wrong, and confidence comes when several independent studies agree.

Myth: A single study settles the question.
Reality: One study rarely proves anything. Results from small or first-time studies often shrink or vanish when repeated, and only about one in three highly cited animal studies were later confirmed in human trials. Look for systematic reviews and guidelines.

Myth: "Statistically significant" means the effect is big or important.
Reality: Statistical significance only means the result would be unlikely by chance if there were no real effect.

The American Statistical Association states that a p-value doesn't measure the size or importance of an effect. A huge study can find a "significant" difference too small to notice.

Myth: "Cuts your risk by 50%" tells you how much a treatment will help.
Reality: That's relative risk. If the starting risk is tiny, a 50% cut may mean very few people actually benefit. Always look for the absolute numbers, such as 12% versus 40%.

Myth: If a supplement label talks about gut or brain health, the FDA must have checked that it works.
Reality: Supplements don't need FDA approval before they're sold. Structure-function claims like "supports digestive comfort" aren't preapproved, and the label must say the FDA hasn't evaluated the claim.

Your Gut Check

Test yourself. Try each one before you open the answer.

1. Claim Check: "9 out of 10 users say our gut-brain gummies cut their anxiety in half! Backed by science. Doctors don't want you to know."

Grade: Hype. "9 out of 10 users say" is a customer survey, a form of testimonial, and the FTC says testimonials never prove a health product works. "Backed by science" with no study named can't be checked, and "doctors don't want you to know" is a sales tactic. The best probiotic evidence for mood is mixed (one depression questionnaire out of four improved in a 2024 review), and that's for specific strains, not this product. A careful version: "Some probiotic strains have shown small, inconsistent mood effects in early trials. This product hasn't been tested in a published trial."

2. Predict: Sam's cousin posts, "New study: a gut bacterium reversed anxiety in mice! This is the cure!" Sam wonders whether the result will hold up in people. What would you predict, and why?

The odds are against a smooth translation. Only about one in three highly cited animal studies were later confirmed in human trials, and JB-1, which calmed anxious mice, had no effect in 29 healthy men. Mouse "anxiety" is measured with behaviors like avoiding open spaces, a rough stand-in for human anxiety. The honest prediction: possibly, but probably less dramatically, and it needs human trials. Calling it a cure is Hype.

3. Explain: A study of 50,000 adults finds that people who take a certain supplement have "statistically significantly" lower stress scores ($p < 0.001$). The difference was 0.3 points on a 40-point scale. Explain why this result might not matter.

With 50,000 people, even a tiny difference can reach significance. A p-value says the difference is unlikely to be pure chance, not that it's large; 0.3 points on a 40-point scale is probably too small for anyone to notice. It's also observational, so supplement takers might differ in other ways (income, exercise, sleep) that explain the gap. Significant, tiny, and not proof of cause.

4. Apply: An ad says a gut supplement "reduces the risk of getting a cold by 50%." The fine print says 4% of people taking a placebo got a cold during the study, compared with 2% of people taking the supplement. Calculate the absolute risk difference and the number needed to treat, and rewrite the claim honestly.

The absolute risk difference is $4\% - 2\% = 2$ percentage points, and the number needed to treat is $1 \div 0.02 = 50$: about 50 people take it for one extra person to avoid a cold. The 50% figure is the relative risk reduction, accurate but bigger-sounding. An honest version: "In one study, 2 out of 100 people taking the supplement caught a cold, compared with 4 out of 100 taking a placebo." You'd still want the study's size, length, and funding. (These numbers are made up for practice.)

5. Read the data. Here are the main results from the ECOSPOR III trial of the oral microbiome treatment SER-109 (later approved as Vowst), from the 2022 *New England Journal of Medicine* abstract (Feuerstadt et al.):

Measure	SER-109 group	Placebo group
Patients enrolled (total)	182 across both groups	
C. diff came back within 8 weeks	12%	40%
Relative risk (SER-109 vs placebo)	0.32 (95% confidence interval, the range the true value likely falls in: 0.18 to 0.58)	
Adverse events (side effects and other health problems during the trial)	Mostly mild to moderate, mostly gut-related, similar numbers in both groups	

5. What does this data show, and what can't it show?

In adults with recurrent C. diff whose symptoms had cleared after antibiotics, the treatment caused a large drop in recurrence: 28 fewer people out of 100, and about one-third the placebo group's risk. Because the trial was randomized and double-blind, we can say the treatment caused the difference. It can't show long-term safety, effects in children or in a first infection, or any effect on other conditions like anxiety or IBS. The maker paid for the trial, so independent studies or longer real-world follow-up would add confidence.

Exercises

Remember

1. List the levels of the hierarchy of evidence from weakest to strongest, as shown in Section 20.3.

Answer

Testimonials, anecdotes, and expert opinion; lab and animal studies; case reports and case series; observational studies; randomized controlled trials; systematic reviews and meta-analyses.

1. What is a preprint, and what warning does the medRxiv server give about preprints?

Answer

A preprint is a complete scientific paper posted publicly before peer review. medRxiv warns that preprints are preliminary, haven't been certified by peer review, shouldn't guide health decisions, and shouldn't be reported in the news as established information.

Understand

1. Explain the difference between a structure-function claim and a disease claim, using one example of each.

Answer

A structure-function claim says a product supports normal body function, such as "supports digestive comfort." It isn't preapproved by the FDA and needs a disclaimer on supplement labels. A disease claim says a product treats, cures, or prevents a disease, such as "treats IBS," and only an approved drug can legally make it.

1. Explain why preregistration makes a study's results more trustworthy.

Answer

Preregistration records the question, main outcome, and analysis plan before the results are known. That stops researchers, even honest ones, from picking whichever outcome happened to look good afterward, and it lets readers check whether the reported outcome matches the planned one.

Apply

1. Find a real gut-health product ad or post (on social media, in a store, or online). Identify whether its claims are structure-function claims or disease claims, find the FDA disclaimer if there is one, and grade the main claim using the Hype Meter. Record where and when you found it.
2. A headline says, "Drinking kombucha linked to 40% lower risk of depression." Using the claim-checking method, list the first four questions you'd ask and which answers would raise or lower your grade.

Analyze

1. Fill in the six questions for the Bravo 2011 mouse study and the Kelly 2017 human trial of JB-1. Analyze why both can be good science despite different conclusions.
2. The book grades "Implanted vagus nerve stimulation is FDA approved for treatment-resistant depression" as Strong and "Vagus nerve stimulation can calm Crohn's disease" as Preliminary. Analyze why the same technology earns two grades.

Evaluate

1. A classmate argues: "Industry-funded studies are always biased, so we should ignore them." Using the Lundh 2017 review and the ECOSPOR III trial, write a paragraph judging this argument. Where is it partly right, and where does it go too far?
2. Pick one claim from the table in Section 20.12 and decide whether you agree with the book's grade. Defend your judgment using at least three of the six questions, and describe one future study that would change your mind.

Create

1. Complete a full student research project (Section 20.14) on a gut-brain claim you've seen online. Include the claim, at least three sources, a six-question table, the numbers, your grade, a 100- to 150-word plain-language summary, and a reference list.
2. Design a 30-second video script or a one-page poster that teaches younger students (grades 6 to 8) one skill from this chapter, such as relative versus absolute risk or spotting a structure-function claim. Use the science communication word ladder so your own claims match the evidence.

Key Takeaways

- The hierarchy of evidence ranks studies by how well they test cause in people: testimonials and animal studies near the bottom, randomized trials and good systematic reviews near the top. A review is only as good as the studies inside it.
- Mouse-to-human translation often fails: only about one in three highly cited animal studies were confirmed in human trials, and the stress probiotic that calmed mice did nothing in healthy men.
- Peer review is a quality check, not a guarantee. Preprints haven't been reviewed yet. Preregistration makes studies more trustworthy by fixing the plan in advance.
- "Statistically significant" doesn't mean big or important. Always ask for the actual group numbers, and convert relative risk into absolute differences and the number needed to treat.

- Conflicts of interest are linked to more favorable results, so they're a reason to look harder, not a reason to dismiss a study automatically.
- Supplement labels can make structure-function claims without FDA approval, and testimonials never prove a health product works.
- The claim-checking method (pin down the claim, trace the source, ask the six questions, check the numbers, zoom out, grade, rewrite) works on any health claim, and good science communication matches words to evidence.

You're a scientist now



You've traveled the whole gut-brain axis with me, from enteric neurons to clinical trials, and now you can grade claims on your own. That's the end of our trip together, but not the end of the science: keep using the method, try the Hype Meter Sorter again, and let's keep checking what the gut is really telling the brain!

Quiz: Be Your Own Scientist: Reading Health Claims

Test your understanding of Chapter 20. Choose the best answer, then click **Show Answer** to check.

Question 1

What is a preprint?

A. A short summary at the top of a published paper

B. A complete scientific paper shared publicly before it has been peer reviewed

C. A company announcement written to attract news coverage

D. A plan for a trial, recorded in a registry before the trial starts

Show Answer

The correct answer is **B**. A preprint is a full paper posted online (for example, on medRxiv) before peer review, and medRxiv itself warns that preprints shouldn't guide health decisions. Option D describes preregistration, a different idea: it records the plan, not the finished paper.

Concept Tested: Preprint **Bloom's Level:** Remember

Question 2

According to a 2007 article by Hackam, about how many highly cited animal studies were later confirmed in human randomized trials?

A. Almost all of them

B. About nine in ten

C. About two in three

D. About one in three

Show Answer

The correct answer is **D**. Hackam summarized that only about one in three highly cited animal studies translated into confirmed results in human trials. Many people assume most animal findings carry over (options A to C), which is exactly why "a study in mice found..." deserves caution.

Concept Tested: Mouse-to-Human Translation **Bloom's Level:** Remember

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Question 3

Which of these is a structure-function claim, the kind a US dietary supplement label can make without FDA approval (along with a disclaimer)?

A. "Supports digestive comfort"

B. "Treats irritable bowel syndrome"

C. "Cures anxiety"

D. "Prevents Crohn's disease flares"

Show Answer

The correct answer is **A**. A structure-function claim describes support for normal body function without claiming to treat, cure, or prevent a disease. Options B, C, and D are disease claims, which only an approved drug can legally make. The label must also say the FDA hasn't evaluated the claim.

Concept Tested: Structure-Function Claim **Bloom's Level:** Remember

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Question 4

Why does preregistering a trial make its results more trustworthy?

A. It guarantees that the trial's main result will be statistically significant.

B. It means the trial was paid for by a government agency instead of a company.

C. It records the main outcome and analysis plan before the results are known, so researchers can't quietly pick whichever outcome looked best.

D. It means peer reviewers have already approved the paper.

Show Answer

The correct answer is **C**. Preregistration fixes the question, main outcome, and analysis plan in advance, which separates planned tests from after-the-fact findings. It says nothing about who paid (B) and doesn't guarantee a positive result (A) or replace peer review (D).

Concept Tested: Preregistration **Bloom's Level:** Understand

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Question 5

A headline says a supplement "significantly reduced stress ($p < 0.01$)." Which statement best explains what "statistically significant" tells you?

A. The supplement had a large effect that most people would notice.

B. A difference this big would be unlikely by chance alone if the supplement truly did nothing, but it doesn't tell you how big or important the effect is.

C. The study has been confirmed by other independent research teams.

D. There is less than a 1% chance that the supplement works.

Show Answer

The correct answer is **B**. Statistical significance means the result would be surprising if there were no real effect. The American Statistical Association's 2016 statement says a p-value does not measure the size or importance of an effect, so option A is the classic mistake. Option D misreads what a p-value means.

Concept Tested: Statistical Significance **Bloom's Level:** Understand

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Question 6

What does peer review usually do?

A. Independent experts check a paper's methods, reasoning, and conclusions before a journal publishes it, though they rarely see the raw data or repeat the experiment.

B. Independent labs repeat the experiment to confirm the result before it is published.

C. The FDA reviews the study and approves the treatment.

D. It proves that the paper's conclusion is true.

Show Answer

The correct answer is **A**. Peer review is a quality check by experts, like a building inspector who can't test every wire behind the walls. It isn't replication (B), regulatory approval (C), or proof (D); peer-reviewed studies can still be wrong, as the JB-1 mouse and human studies showed.

Concept Tested: Peer Review **Bloom's Level:** Understand

Question 7

In the ECOSPOR III trial, C. diff came back in 12% of people who took the microbiome treatment and 40% of people who took a placebo. What is the absolute risk difference?

A. 12%

B. 68%

C. 0.32

D. 28 percentage points

Show Answer

The correct answer is **D**. The absolute difference is $40\% - 12\% = 28$ percentage points, meaning 28 fewer people out of every 100 had a recurrence. Option C (0.32) is the relative risk, and option B (68%) is the relative risk reduction. Both are accurate, but they describe the change as a ratio, not as actual numbers of people.

Concept Tested: Absolute vs Relative Risk **Bloom's Level:** Apply

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Question 8

Sam's cousin shares a post: "Peer-reviewed study proves this probiotic cures anxiety!" Sam traces it to the paper and finds it was done in 12 mice, with no human data. Using the Hype Meter, what is the best grade for the post's claim as stated?

A. Strong, because the study was peer reviewed

B. Moderate, because it shows a real effect in animals

C. Hype, because a small mouse study is stretched into a claim that it cures anxiety in people

D. It can't be graded without knowing who paid for the study

Show Answer

The correct answer is **C**. The underlying mouse result might be interesting (Preliminary at most), but the post claims a proven human cure, which the evidence doesn't support. Peer review (A) doesn't turn a mouse study into human proof, and funding (D) matters but isn't needed to see that this claim far outruns its evidence.

Concept Tested: Claim-Checking Method **Bloom's Level:** Apply

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Question 9

A 2017 Cochrane review (Lundh and colleagues) found that studies sponsored by the company making the product more often reported favorable results. Which conclusion best fits this finding?

A. Company funding is a conflict of interest that calls for a closer look at design, registration, and independent confirmation, but it doesn't automatically make a study wrong.

B. All industry-funded studies are fake and should be ignored.

C. Funding has no effect on research results, so readers can skip the funding statement.

D. Only government agencies are allowed to fund clinical trials.

Show Answer

The correct answer is **A**. The review linked industry sponsorship to more favorable results and conclusions, so a conflict of interest is a reason to look harder. But most new medicines are tested in company-funded trials, and well-designed ones (like ECOSPOR III, which was randomized, blinded, and preregistered) can still be strong evidence. Option B overcorrects; option C ignores the evidence.

Concept Tested: Conflict of Interest **Bloom's Level:** Analyze

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Question 10

A news story says a new IBD pill "puts Crohn's into remission." The company press release cites a trial in adults whose planned main outcome was a symptom score at 12 weeks, and the results aren't yet peer reviewed. What is the most important difference between the press release and the trial record?

A. The press release is more trustworthy because it was written by the company's experts.

B. The trial record shows a narrower result (a symptom score in adults at 12 weeks) than the headline's broad promise of "remission" for anyone with Crohn's.

C. There is no difference; press releases and trial records always report the same thing.

D. The trial record proves the pill doesn't work.

Show Answer

The correct answer is **B**. Reading the abstract or registry shows who was studied, what was measured, and for how long, and here those are much narrower than the headline. A press release is written to attract attention (so A is wrong), and a narrow result doesn't mean the pill fails (D); it means the claim must match what was actually tested.

Concept Tested: Reading an Abstract **Bloom's Level:** Analyze

Glossary

Every key term in this book, defined in plain words, with an example and a link to the chapter that teaches it.

A · B · C · D · E · F · G · H · I · J · K · L · M · N · O · P · Q · R · S · T · U · V · Z · 1 · 5

1

16S rRNA Sequencing

A method for identifying bacteria in a sample by reading the DNA of one marker gene, the 16S ribosomal RNA gene, which all bacteria have and which differs between groups.

Example: Like reading product barcodes, 16S rRNA sequencing shows roughly which bacteria are present, but not what each one can do.

See also: Metagenomic Sequencing

Taught in Chapter 3: Meet the Microbiome.

5

504 Plan

A written plan, developed by the school with the student and their parents or guardians, that lists the accommodations a student with a disability needs for equal access to education, under Section 504 of the Rehabilitation Act of 1973.

Example: A 504 plan for a student with Crohn's disease could include restroom access, rest breaks, and extra time.

See also: School Accommodation

Taught in Chapter 19: Culture, Food, Family, and Stigma.

A

Absolute vs Relative Risk

The difference between two ways of describing how much a treatment changes the chance of an outcome: absolute risk is the actual chance in a group, and relative risk compares the groups as a ratio, which can

sound large even when the actual numbers are small.

Example: In the Vowst trial, recurrence was 12.4% versus 39.8% with placebo at 8 weeks, an absolute drop of about 27 percentage points, which sounds even bigger described as a relative reduction.

See also: Statistical Significance, Health Claim Marketing

Taught in Chapter 20: Be Your Own Scientist: Reading Health Claims.

Acetate

The two-carbon short-chain fatty acid, usually the most abundant one. It travels farthest, passing through the liver and reaching the rest of the body in the blood.

Example: Acetate is the short-chain fatty acid most likely to reach the brain's blood supply.

See also: Short-Chain Fatty Acid, Butyrate

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

Acetylcholine

A neurotransmitter that activates muscles and many glands. In the gut it is the main "go" signal enteric motor neurons use to make smooth muscle contract, and it is the main chemical the vagus nerve releases onto its targets.

Example: An excitatory enteric motor neuron releases acetylcholine to start a contraction during peristalsis.

See also: Neurotransmitter, Vagus Nerve

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Acute Stress

Short-term stress from a single challenge, in which the stress response switches on and then returns to baseline within minutes to hours once the challenge ends.

Example: The nerves Sam feels at the starting line of a race are acute stress.

See also: Chronic Stress, Stress Response

Taught in Chapter 7: Stress and the Gut.

Adaptive Immunity

The slower but highly specific part of the immune system, run by T cells and B cells, that learns to recognize particular invaders and keeps a memory so it responds faster the next time.

Example: B cells in the gut that become plasma cells and make antibodies against a specific microbe are part of adaptive immunity.

See also: Innate Immunity, Regulatory T Cell

Taught in Chapter 4: The Immune System as a Sense Organ.

Adrenal Gland

A small gland on top of each kidney, with an outer cortex that makes steroid hormones like cortisol and an inner medulla that makes epinephrine and norepinephrine.

Example: The adrenal glands release cortisol when ACTH reaches them through the blood.

See also: Cortisol, Hypothalamic-Pituitary-Adrenal (HPA) Axis

Taught in Chapter 7: Stress and the Gut.

Adrenocorticotropic Hormone (ACTH)

A hormone released by the anterior pituitary into the blood that travels to the adrenal glands and tells their outer layer to make cortisol.

Example: When the pituitary releases more ACTH during stress, the adrenal glands soon make more cortisol.

See also: Pituitary Gland, Cortisol

Taught in Chapter 7: Stress and the Gut.

Afferent Signal

A signal carried by nerve fibers toward the central nervous system, usually sensory information from the body. A memory trick: afferent arrives.

Example: A message that the stomach is stretched, traveling up the vagus nerve to the brainstem, is an afferent signal.

See also: Efferent Signal, Vagus Nerve

Taught in Chapter 2: The Vagus Highway.

Alarm Features

Symptoms, signs, or history that suggest a disease other than IBS, such as inflammation, bleeding, or cancer, and that call for further medical evaluation.

Example: Blood in the stool, unexplained weight loss, and anemia are alarm features.

See also: Positive Diagnosis Strategy, Irritable Bowel Syndrome

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

Alpha-Synuclein

A protein found in neurons, especially at their signaling tips, that can misfold and clump together. These clumps are a hallmark of Parkinson's disease.

Example: Even healthy human appendixes have been found to contain clumped alpha-synuclein.

See also: Lewy Body, Prion-Like Spread

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Alzheimer's Disease

A progressive brain disease that slowly destroys memory and thinking skills and, eventually, the ability to carry out everyday tasks. It is the most common cause of dementia in older adults.

Example: More than 6 million Americans, most aged 65 or older, may have Alzheimer's disease.

See also: Amyloid Beta, Neurodegeneration

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Aminosalicylate

An anti-inflammatory medicine that works on the gut lining, used mainly for mild to moderate ulcerative colitis. It is also called a 5-ASA drug.

Example: Mesalamine is an aminosalicylate, a long-established medicine for ulcerative colitis.

See also: Ulcerative Colitis, Corticosteroid

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Amyloid Beta

A small protein fragment, cut from a larger protein in the brain, that can clump into sticky plaques between neurons. These plaques are one of the main signs of Alzheimer's disease.

Example: Amyloid beta plaques can begin forming a decade or more before memory problems appear.

See also: Alzheimer's Disease

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Animal Model

A non-human animal, such as a mouse or rat, used to study a biological process or disease because it shares key features with humans and can be studied in ways not possible in people.

Example: Researchers use a mouse animal model to test whether a gut bacterium changes behavior, because they can control the mouse's diet and genes.

See also: Germ-Free Mouse, Mouse-to-Human Translation

Taught in Chapter 3: Meet the Microbiome.

Anterior Cingulate Cortex

A strip of cortex near the front of the brain, along the midline, that helps give pain its unpleasant, emotional "I need to do something" quality and helps focus attention on it. It is often shortened to ACC.

Example: Worrying about a cramp during class engages the anterior cingulate cortex, which makes the pain feel more urgent.

See also: Insula, Pain Perception

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Anti-TNF Therapy

A type of biologic treatment that blocks tumor necrosis factor, a cytokine that drives inflammation in IBD. Anti-TNF medicines were the first biologics approved for IBD.

Example: Infliximab and adalimumab are anti-TNF therapies.

See also: Tumor Necrosis Factor, Biologic Therapy

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Antibiotic Disruption

The change in the gut microbiota caused by antibiotics: a loss of bacterial numbers and diversity, shifts in which groups dominate, and a recovery afterward that is often fast but not always complete.

Example: After a course of antibiotics for strep throat, a person's gut diversity may drop and take weeks to recover.

See also: Colonization Resistance, C. difficile Infection

Taught in Chapter 3: Meet the Microbiome.

Anxiety Disorder

A mental health condition in which worry, fear, or nervousness does not go away, shows up in many situations, and can get worse over time, interfering with daily life.

Example: Generalized anxiety disorder, panic disorder, and social anxiety disorder are types of anxiety disorder.

See also: GI-Specific Anxiety, Psychiatric Comorbidity

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Appendix and Parkinson's

The research question of whether removing the appendix changes a person's later risk of Parkinson's disease, based on the idea that the appendix might store misfolded alpha-synuclein that could seed the disease.

Example: One large study linked appendix removal to lower Parkinson's risk, while a Danish study of 265,758 people found slightly higher risk, so the question of the appendix and Parkinson's is still open.

See also: Braak Hypothesis, Gut-First Subtype

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Attention-Deficit/Hyperactivity Disorder (ADHD)

A neurodevelopmental condition involving ongoing patterns of inattention, hyperactivity, and/or impulsivity that show up in more than one setting and affect daily life.

Example: A student with ADHD may struggle to stay focused on homework at home and in class, not just in one setting.

See also: Neurodiversity, Autism

Taught in Chapter 13: Autism, ADHD, and the Gut.

Autism

A lifelong neurodevelopmental difference that affects how a person communicates and interacts with others, processes sensory information, and experiences the world, often including focused interests and repetitive behaviors.

Example: An autistic teen may find loud cafeterias overwhelming and have a deep, focused interest in trains.

See also: Neurodiversity, Identity-First Language, GI Symptoms in Autism

Taught in Chapter 13: Autism, ADHD, and the Gut.

Autonomic Nervous System

The automatic, involuntary part of the nervous system that controls internal organs, glands, and smooth muscle. It has a sympathetic branch and a parasympathetic branch.

Example: Your heart rate rising during a race and your gut slowing down both happen through the autonomic nervous system, without you deciding.

See also: Sympathetic Nervous System, Parasympathetic Nervous System

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

B

Bacteria-to-Human Cell Ratio

The number of bacterial cells in a person's body divided by the number of human cells. A typical adult has roughly 38 trillion bacterial cells and 30 trillion human cells, about 1.3 to 1.

Example: The old "10 to 1" figure for the bacteria-to-human cell ratio is wrong.

See also: Gut Microbiota

Taught in Chapter 3: Meet the Microbiome.

Bacterial Strain

A genetic variant within a single bacterial species. Strains of the same species share most of their genes but differ in some, which can change what they do.

Example: Most strains of *E. coli* are harmless, but a few strains can cause serious illness.

See also: Strain Specificity, Pathogen

Taught in Chapter 3: Meet the Microbiome.

Balloon Distension Test

A research and specialty test in which a thin, soft balloon in the rectum or colon is inflated with set volumes or pressures while the person reports when they first feel it, when it is uncomfortable, and when it hurts.

Example: A balloon distension test can show that a person with IBS feels pain at a lower volume than average.

See also: Visceral Hypersensitivity

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Behavior Change

The process of adopting and keeping a new health habit, usually by setting small, specific goals, tracking them, and adjusting based on what you learn.

Example: Moving bedtime 15 minutes earlier each week, rather than changing everything at once, is a realistic behavior change plan.

See also: Self-Monitoring, Sleep Hygiene

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Benefit-Risk Balance

The weighing of how much a treatment is likely to help against how likely and how serious its harms are, for a particular person and a particular condition.

Example: An implanted device that needs surgery has a better benefit-risk balance for severe, drug-resistant epilepsy than for mild stress.

See also: Shared Decision-Making, FDA Approval

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Bidirectional Relationship

A connection between two things in which each one can influence the other, so changes can flow in both directions.

Example: Gut symptoms can worsen mood, and anxiety can worsen gut symptoms, a bidirectional relationship.

See also: Gut-Brain Axis, Reverse Causation

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Bifidobacterium

A large group of bacteria that live naturally in the human gut and ferment sugars and some fibers.

Example: Human milk oligosaccharides feed *Bifidobacterium*, so this group often dominates a breastfed infant's gut.

See also: Lactobacillus, Human Milk Oligosaccharides

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Bioelectronic Medicine

An approach to treatment that uses electrical stimulation of nerves, instead of or alongside drugs, to change how organs or the immune system work.

Example: The SetPoint System, the first approved device designed to treat an autoimmune disease by stimulating the vagus nerve, is a milestone for bioelectronic medicine.

See also: Inflammatory Reflex, Implanted VNS Device

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Biologic Therapy

Treatment with a medicine made by living cells, usually a lab-made antibody, that blocks one specific immune signal or cell pathway involved in inflammation.

Example: Riya takes biologic therapy by injection to keep her Crohn's in remission.

See also: Anti-TNF Therapy, JAK Inhibitor

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Birth Mode and Microbes

The way a baby's delivery, vaginal birth or cesarean section, shapes which microbes first colonize the newborn's gut.

Example: Babies born by C-section tend at first to carry more skin-type microbes than babies born vaginally.

See also: Microbiome Development

Taught in Chapter 3: Meet the Microbiome.

Blood-Brain Barrier

The specialized lining of the brain's blood vessels, made of tightly sealed endothelial cells supported by other cells, that tightly controls which ions, molecules, and cells pass from the blood into the brain. It is often shortened to BBB.

Example: Serotonin made in the gut does not cross the blood-brain barrier, but tryptophan can.

See also: Blood-Brain Barrier Permeability, Circumventricular Organ

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Blood-Brain Barrier Permeability

How easily substances can pass from the blood into the brain across the blood-brain barrier. Higher permeability means a "leakier" barrier.

Example: In mice, germ-free animals had higher blood-brain barrier permeability than normal mice, and gut bacteria or butyrate helped tighten it.

See also: Blood-Brain Barrier, Germ-Free Mouse

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

Braak Hypothesis

The proposal, published by Heiko Braak and colleagues in 2003, that Parkinson's pathology spreads through the nervous system in a predictable order, beginning low in the brainstem and in the smell system, and in some cases may start in the gut and travel up the vagus nerve.

Example: The Braak hypothesis predicts that cutting the vagus nerve might lower Parkinson's risk, which researchers tested in vagotomy studies.

See also: Prion-Like Spread, Truncal Vagotomy Studies, Gut-First Subtype

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Brain-First Subtype

A proposed form of Parkinson's disease in which alpha-synuclein pathology starts inside the brain, reaches the dopamine system early, and spreads down to the brainstem and body nerves later.

Example: A person whose tremor appears first, with gut problems only later if at all, fits the brain-first subtype.

See also: Gut-First Subtype

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Brain-Gut Psychotherapy

The family of psychological treatments designed specifically for gut conditions, which target how the brain processes gut signals, how stress and worry change gut function, and how fear of symptoms leads to avoidance.

Example: Gut-focused CBT and gut-directed hypnotherapy are both forms of brain-gut psychotherapy.

See also: Cognitive Behavioral Therapy, Gut-Directed Hypnotherapy

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Brainstem

The stalk of brain tissue that connects the rest of the brain to the spinal cord, made of the midbrain, the pons, and the medulla.

Example: Signals from the vagus nerve arrive first in the medulla, the lowest part of the brainstem.

See also: Nucleus Tractus Solitarius, Dorsal Motor Nucleus

Taught in Chapter 2: The Vagus Highway.

Butyrate

The four-carbon short-chain fatty acid. Most of it never leaves the gut wall, because colonocytes use it as their fuel.

Example: Butyrate made by colon bacteria from fiber feeds the cells lining the colon.

See also: Colonocyte, Gene Regulation by Butyrate

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

C

C. difficile Infection

An infection of the colon by the bacterium *Clostridioides difficile* that causes diarrhea and colon inflammation and can be life-threatening. It most often follows antibiotics that wipe out the normal bacteria that keep it in check. It is often shortened to CDI.

Example: A person who develops severe diarrhea a week after taking antibiotics may be tested for C. difficile infection.

See also: Antibiotic Disruption, Fecal Microbiota Transplant, Live Biotherapeutic Product

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Caregiver Role

The set of responsibilities family members take on for someone with a health condition, such as managing appointments and medicines, preparing food, giving emotional support, and advocating with schools, along with the stress that can come with it.

Example: As a teen grows older, the caregiver role often shifts from parents to the teen, who gradually manages their own medicine and appointments.

See also: Family Communication

Taught in Chapter 19: Culture, Food, Family, and Stigma.

Celiac Disease

A lifelong, immune-driven disorder in which eating gluten triggers the immune system to damage the lining of the small intestine.

Example: Celiac disease affects about 1% of people worldwide and about 2 million people in the US.

See also: Gluten, Villous Atrophy, Gluten-Free Diet

Taught in Chapter 12: Celiac Disease and Food Reactions.

Central Nervous System

The brain and spinal cord, which together form the body's main processing center. It is often shortened to CNS.

Example: A signal from the gut that reaches the brainstem has entered the central nervous system.

See also: Peripheral Nervous System, Enteric Nervous System

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Central Sensitization

An increase in the excitability of pain-processing neurons in the spinal cord and brain, so that normal or weak incoming signals produce stronger pain responses.

Example: After long-lasting gut pain, central sensitization can make ordinary digestion feel painful even when the gut tissue looks normal.

See also: Peripheral Sensitization, Visceral Hypersensitivity

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Cholecystokinin

A gut hormone released by enteroendocrine cells in the small intestine, mainly after protein-rich and fat-rich food, that helps digest food and acts as a satiety signal partly by exciting vagal sensory nerves. It is often shortened to CCK.

Example: Cholecystokinin was named for making the gallbladder contract, which squeezes bile into the intestine to help digest fat.

See also: Gut Hormone, Satiety Signal

Taught in Chapter 2: The Vagus Highway.

Chronic Stress

Stress that lasts for weeks or months, or keeps returning before the body has recovered, so the stress systems stay switched on or are repeatedly reactivated.

Example: Months of ongoing family conflict or bullying can cause chronic stress.

See also: Acute Stress, Early-Life Stress

Taught in Chapter 7: Stress and the Gut.

Circadian Rhythm

A roughly 24-hour cycle in the body's functions, such as sleepiness, body temperature, hormone release, and digestion, driven by an internal clock and kept in step with the outside world, mostly by light.

Example: Feeling sleepy at night and alert in the morning reflects your circadian rhythm.

See also: Microbiome Daily Rhythm, Sleep Architecture

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Circumventricular Organ

One of several small brain regions around the fluid-filled ventricles that lack a complete blood-brain barrier, letting them sample the blood directly.

Example: Cytokines in the blood can be detected at a circumventricular organ even though they cannot cross the rest of the blood-brain barrier.

See also: Blood-Brain Barrier, Immune-to-Brain Signaling

Taught in Chapter 4: The Immune System as a Sense Organ.

Claim-Checking Method

This book's step-by-step process for judging a health claim: state the exact claim, trace it to its original source, ask the six questions, check the numbers and the money, weigh it against the wider evidence, and assign a Hype Meter grade with a careful rewrite.

Example: Using the claim-checking method, a student traces a supplement ad to a small mouse study, checks who paid for it, and grades the claim Preliminary or Hype.

See also: Hype Meter, Reading an Abstract

Taught in Chapter 20: Be Your Own Scientist: Reading Health Claims.

Clinical Trial Phases

A series of increasingly large studies in people that test a new treatment first for safety, then for whether it works, then how it compares at a large scale, with monitoring continuing after approval.

Example: A Phase 1 trial might include about 20 to 100 people, while a Phase 3 trial might include about 300 to 3,000.

See also: FDA Approval, Randomized Controlled Trial

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Cognitive Behavioral Therapy

A structured, skills-based form of talk therapy that helps people notice and change unhelpful thought patterns and behaviors, which can reduce symptoms and their impact. It is often shortened to CBT.

Example: In cognitive behavioral therapy for IBS, a teen practices replacing "I'll have an accident in class" with a more balanced thought.

See also: Brain-Gut Psychotherapy, Pain Catastrophizing

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

Cohort Study

A study that follows a group of people over time, measuring things at the start and again later, to see which earlier factors predict later outcomes.

Example: In one cohort study, higher anxiety at the start predicted a new functional gut disorder 12 years later, evidence for a brain-to-gut direction.

See also: Observational Study, Reverse Causation

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Colonization Resistance

The ability of the normal gut microbiota to keep harmful microbes from settling in and multiplying, by competing for space and nutrients, making blocking substances, and stimulating the body's defenses.

Example: When antibiotics weaken colonization resistance, *C. difficile* can take over the colon.

See also: Commensal Bacteria, Antibiotic Disruption

Taught in Chapter 3: Meet the Microbiome.

Colonocyte

One of the epithelial cells lining the inside of the colon, which absorb water and salts and help form the barrier between gut contents and the body.

Example: Colonocytes get much of their energy from butyrate made by gut bacteria.

See also: Butyrate, Intestinal Epithelium

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

Colonoscopy

A procedure in which a doctor passes a long, thin, flexible tube with a light and camera through the anus to look at the lining of the rectum and colon, and often the end of the small intestine, usually under sedation.

Example: During a colonoscopy, the doctor takes small tissue samples (biopsies) to confirm IBD.

See also: Mucosal Healing, Fecal Calprotectin

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Colony-Forming Unit

A count of how many microbes in a sample are alive and able to multiply, measured by growing a diluted sample on nutrient gel and counting the colonies. It is often shortened to CFU.

Example: A label that brags "50 billion colony-forming units" tells you how many live microbes it contains, not whether they help you.

See also: Probiotic

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Commensal Bacteria

Bacteria that normally live on or in the body without causing harm, and often provide benefits such as helping digest fiber or crowding out harmful microbes.

Example: Commensal bacteria in the colon ferment fiber you cannot digest into short-chain fatty acids.

See also: Colonization Resistance, Pathogen

Taught in Chapter 3: Meet the Microbiome.

Conflict of Interest

A situation in which a researcher, author, or organization has financial or personal ties, such as funding, a job, stock, or a patent, that could influence, or seem to influence, how research is designed, interpreted, or reported.

Example: A probiotic trial paid for and run by the company that sells the probiotic has a conflict of interest worth noting.

See also: Health Claim Marketing, Preregistration

Taught in Chapter 20: Be Your Own Scientist: Reading Health Claims.

Confounding Variable

A third factor that affects both things being studied, creating a link between them even if neither causes the other.

Example: Poor sleep could worsen both mood and gut symptoms, making it a possible confounding variable in gut-mood research.

See also: Correlation vs Causation, Mediator Variable, Diet as Confounder

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Constipation

Having fewer bowel movements than usual (often fewer than three a week), or stools that are hard, dry, or difficult to pass.

Example: About 16 out of 100 adults have constipation symptoms, usually from ordinary causes like low fiber or too little fluid.

See also: Prodromal Symptoms, Dietary Fiber

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Consumer Wellness Device

A product sold directly to the public that claims to support general health or well-being, such as relaxation or stress relief, and is marketed without having to show the FDA that it treats any disease.

Example: An ear clip sold online to "tone your vagus nerve for calm" is a consumer wellness device, not an FDA-approved treatment.

See also: Noninvasive VNS, Health Claim Marketing

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Correlation vs Causation

The distinction between two things happening together (a correlation, or association) and one thing actually producing the other (causation).

Example: People with depression have different gut microbes on average, but that correlation alone does not show the microbes caused the depression.

See also: Reverse Causation, Confounding Variable

Taught in Chapter 3: Meet the Microbiome.

Corticosteroid

A powerful, fast-acting medicine related to the body's stress hormone cortisol that broadly calms the immune system. It is often just called a steroid.

Example: Riya had a course of a corticosteroid at diagnosis to calm her Crohn's quickly.

See also: Cortisol, Immunomodulator

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Corticotropin-Releasing Hormone

A hormone made by neurons in the hypothalamus that tells the pituitary gland to release ACTH. It is also made outside the HPA axis, including in the gut wall, and is also called corticotropin-releasing factor (CRF). It is often shortened to CRH.

Example: In animal studies, corticotropin-releasing hormone acting in the colon speeds up colon movement.

See also: Hypothalamic-Pituitary-Adrenal (HPA) Axis, Stress and Gut Motility

Taught in Chapter 7: Stress and the Gut.

Cortisol

The main stress hormone in humans, a steroid made by the adrenal cortex that helps the body handle longer-lasting stress by raising available fuel and calming inflammation, and that shuts down its own production through feedback.

Example: Cortisol levels rise during a stressful week of exams and fall again once the exams end.

See also: Hypothalamic-Pituitary-Adrenal (HPA) Axis, Negative Feedback, Corticosteroid

Taught in Chapter 7: Stress and the Gut.

Cranial Nerve

One of the twelve nerves on each side of the head that connect directly to the brain rather than the spinal cord, numbered I through XII.

Example: The vagus nerve is cranial nerve X, the tenth cranial nerve.

See also: Vagus Nerve, Brainstem

Taught in Chapter 2: The Vagus Highway.

Crisis Resources

Services that give immediate, free support to someone in emotional distress or danger, such as suicide and crisis hotlines, text lines, and emergency rooms.

Example: In the US, you can call or text 988, or chat at 988lifeline.org, to reach the 988 Suicide & Crisis Lifeline, which is free, confidential, and available 24/7.

See also: Help-Seeking

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Crohn's Disease

A form of inflammatory bowel disease that can affect any part of the digestive tract, from mouth to anus, most often the end of the small intestine and the start of the colon, often in patches with healthy sections between.

Example: Riya's Crohn's disease affects the end of her small intestine and part of her colon, the most common pattern.

See also: Transmural Inflammation, Ulcerative Colitis

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Cytokine

A small protein that cells release to send signals to other cells, especially to coordinate immune responses and inflammation.

Example: Interleukin-6 and tumor necrosis factor are cytokines that turn inflammation up.

See also: Interleukin-6, Tumor Necrosis Factor, Interleukin-1 Beta

Taught in Chapter 4: The Immune System as a Sense Organ.

D

Defining a Healthy Microbiome

The scientific challenge of identifying which features of a gut microbial community reliably support health, and what their normal ranges are, given that healthy people's microbiomes differ greatly.

Example: A stool test claiming to compare your microbes to "the healthy microbiome" overlooks that scientists are still defining a healthy microbiome.

See also: Microbial Diversity, Dysbiosis

Taught in Chapter 3: Meet the Microbiome.

Descending Pain Modulation

The brain's ability to turn incoming pain signals down, or up, by sending signals from the brainstem down to the dorsal horn of the spinal cord.

Example: An athlete who does not notice an injury until after a game shows descending pain modulation turning pain down.

See also: Gate Control Theory, Pain Perception

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Diet as Confounder

The idea that differences in what people eat can create an apparent link between a condition and the gut microbiome, because diet shapes the microbiome and may also differ between groups for reasons related to the condition.

Example: If autistic children eat a narrower range of foods, their gut bacteria may differ because of diet, not autism, an example of diet as confounder.

See also: Confounding Variable, Selective Eating

Taught in Chapter 13: Autism, ADHD, and the Gut.

Dietary Fiber

The part of plant foods that human digestive enzymes cannot break down, so it reaches the large intestine mostly intact, where gut microbes can ferment some of it.

Example: Beans, lentils, oats, and vegetables are good sources of dietary fiber.

See also: Fermentation, Dietary Fiber Gap, Prebiotic

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

Dietary Fiber Gap

The difference between how much fiber people actually eat and how much dietary guidelines suggest.

Example: Average US intake is about 16 grams a day, while the 2020 to 2025 guidelines suggested about 25 g for girls and 31 g for boys aged 14 to 18, a large dietary fiber gap.

See also: Dietary Fiber

Taught in Chapter 15: Food and Mood.

Dietary Pattern

The overall combination of foods and drinks a person usually eats over time, studied as a whole instead of one food or nutrient at a time.

Example: The Mediterranean diet is a dietary pattern, not a single food.

See also: Mediterranean Diet, Ultra-Processed Food

Taught in Chapter 15: Food and Mood.

Dietary Supplement Regulation

The set of US rules for products like vitamins, herbs, and most probiotics, which, unlike medicines, do not need FDA approval for safety or effectiveness before they are sold. The main law is the Dietary Supplement Health and Education Act of 1994 (DSHEA).

Example: Under dietary supplement regulation, a probiotic company can start selling its product without first proving to the FDA that it works.

See also: FDA Approval, Structure-Function Claim

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Digestive Tract

The continuous tube that food travels through, from the mouth through the throat, esophagus, stomach, small intestine, and large intestine to the anus. Doctors also call it the gastrointestinal (GI) tract.

Example: In a living adult, the digestive tract is about 7.6 meters (25 feet) long, coiled up inside the abdomen.

See also: Gut Wall Layers, Enteric Nervous System

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Disease Flare

A period when IBD becomes active, with increased inflammation and symptoms such as diarrhea, pain, bleeding, and tiredness.

Example: Riya is mostly in remission but has an occasional disease flare.

See also: Remission, Fecal Calprotectin

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Dopamine

A neurotransmitter the brain uses in movement, motivation, and learning from rewards, which also acts in other parts of the body, including the gut.

Example: In Parkinson's disease, the loss of neurons that make dopamine causes movement symptoms.

See also: Dopamine Neuron Loss, Neurotransmitter

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Dopamine Neuron Loss

The death of dopamine-making neurons in the substantia nigra, the main cause of the movement symptoms of Parkinson's disease.

Example: By the time movement symptoms appear, most people with Parkinson's have already lost 60 to 80% or more of these cells, so dopamine neuron loss starts long before diagnosis.

See also: Parkinson's Disease, Dopamine

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Dorsal Horn

The back part of the spinal cord's gray matter, where incoming sensory neurons form synapses with spinal neurons that carry signals on toward the brain. Signals can be boosted or dampened here.

Example: In gate control theory, the dorsal horn is where touch signals can partly block pain signals.

See also: Gate Control Theory, Central Sensitization

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Dorsal Motor Nucleus

A cluster of neurons in the medulla, next to the nucleus tractus solitarius, whose fibers travel down the vagus nerve to carry motor signals to the stomach and intestines, usually by connecting to enteric neurons.

Example: When you smell dinner, the dorsal motor nucleus can signal the stomach, through the vagus, to get ready.

See also: Efferent Signal, Nucleus Tractus Solitarius

Taught in Chapter 2: The Vagus Highway.

Dorsal Root Ganglion

A cluster of sensory neuron cell bodies just outside the spinal cord, on the nerve root that enters the back side of the cord.

Example: A spinal sensory neuron that detects colon stretch has its cell body in a dorsal root ganglion.

See also: Spinal Afferent Nerve, Dorsal Horn

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Dose-Response Relationship

A pattern in which more of an exposure goes with a steadily larger effect. It makes a causal story more believable but is not proof.

Example: If each extra serving of vegetables went with a slightly lower depression risk, that would be a dose-response relationship.

See also: Confounding Variable, Observational Study

Taught in Chapter 15: Food and Mood.

Dysbiosis

A change in the gut microbiota away from its usual makeup that is thought to be harmful, such as lower diversity, loss of helpful groups, or overgrowth of potentially harmful ones. Scientists warn that the term is slippery.

Example: A study reporting "dysbiosis" in people with a disease usually shows a difference in microbes, not that the difference caused the disease.

See also: Microbial Diversity, Correlation vs Causation

Taught in Chapter 3: Meet the Microbiome.

E

Early-Life Stress

Serious or repeated stress before birth, in infancy, or in childhood, such as separation from caregivers, neglect, or trauma, that may change how the stress system and gut-brain axis respond later in life.

Example: In animals, early-life stress has long-lasting effects on the stress system and the gut; in people, links between early adversity and IBS are associations.

See also: Chronic Stress, Hypothalamic-Pituitary-Adrenal (HPA) Axis

Taught in Chapter 7: Stress and the Gut.

Eating Disorder Risk

The chance of developing an eating disorder, a serious illness marked by severe disturbances in eating behaviors, thoughts, and feelings about food.

Example: Strict food rules and cutting out whole food groups to eat "perfectly" for gut health can be warning signs of eating disorder risk.

See also: Unneeded Restrictive Diet

Taught in Chapter 15: Food and Mood.

Effect Size

A number that describes how big a difference between groups is, often measured in standard deviations, so results from different scales can be compared. An effect size of 0 means no difference.

Example: Two trials using different depression questionnaires can be compared by converting each result into an effect size.

See also: Statistical Significance, Meta-Analysis

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Efferent Signal

A signal carried by nerve fibers away from the central nervous system, out to muscles, glands, or organs, usually a command. A memory trick: efferent exits.

Example: A command from the brainstem telling the stomach to relax and make room for food is an efferent signal.

See also: Afferent Signal, Dorsal Motor Nucleus

Taught in Chapter 2: The Vagus Highway.

Enteric Glia

Non-neuron cells of the enteric nervous system that surround and support enteric neurons and help regulate gut function. Much of the evidence for their roles in reflexes, the barrier, and immunity comes from animals.

Example: Scientists once thought enteric glia were just packing material, but that view has been refuted.

See also: Enteric Neuron, Microglia

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Enteric Nervous System

The network of neurons and support cells built into the wall of the digestive tract, from the esophagus to the anus. It can run gut reflexes without input from the brain or spinal cord.

Example: The enteric nervous system can still push food along a loop of intestine even after its connections to the brain are cut.

See also: Myenteric Plexus, Submucosal Plexus, Enteric Nervous System Neuron Count

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Enteric Nervous System Neuron Count

The estimated total number of neurons in the human enteric nervous system: hundreds of millions, about 400 to 600 million by common estimates, roughly as many as the spinal cord.

Example: The brain has about 86 billion neurons, so the enteric nervous system neuron count is far smaller than the brain's.

See also: Enteric Nervous System, Second Brain Metaphor

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Enteric Neuron

A nerve cell whose cell body sits in one of the ganglia of the gut wall. Enteric neurons include sensory neurons, interneurons, and motor neurons, up to about 20 types in all.

Example: An excitatory enteric motor neuron releases acetylcholine to make gut smooth muscle contract.

See also: Enteric Nervous System, Enteric Glia

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Enterochromaffin Cell

A type of enteroendocrine cell in the gut lining that senses conditions inside the gut and releases serotonin, making most of the body's serotonin with the enzyme TPH1. It is often shortened to EC cell.

Example: When food stretches the intestine, enterochromaffin cells release serotonin that activates nearby nerve endings.

See also: Serotonin, Enteroendocrine Cell

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Enteroendocrine Cell

A hormone-releasing sensor cell scattered among the lining cells of the stomach and intestines that detects nutrients and other substances and responds by releasing hormones and other signals. These cells make up about 1% of intestinal lining cells.

Example: When fat reaches the small intestine, enteroendocrine cells release cholecystokinin.

See also: Gut Hormone, Neuropod Cell, Enterochromaffin Cell

Taught in Chapter 2: The Vagus Highway.

Evidence Grade

A rating that summarizes how strong and how direct the scientific support for a specific claim is, as the claim is actually stated.

Example: A claim backed mostly by small mouse studies earns an evidence grade of Preliminary.

See also: Hype Meter, Hierarchy of Evidence

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Exercise and Gut Transit

The way physical activity changes how quickly food and waste move through the digestive tract, along with related changes in blood flow and the gut lining. The effect depends heavily on how hard and how long a person exercises.

Example: Easy runs seem to settle Sam's stomach, while hard race-day efforts sometimes send him sprinting for a porta-potty, two sides of exercise and gut transit.

See also: Physical Activity, Stress and Gut Motility

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Exercise and Mood

The effects of physical activity on emotional well-being, including symptoms of depression, anxiety, and stress.

Example: An umbrella review of 1,039 trials found that physical activity programs had medium-sized benefits for depression, strong evidence on exercise and mood.

See also: Physical Activity, Major Depressive Disorder

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Extraintestinal Manifestation

A sign of IBD that shows up outside the intestines, such as joint pain, skin problems, eye inflammation, or liver problems.

Example: Painful, swollen knees during a Crohn's flare are an extraintestinal manifestation.

See also: Inflammatory Bowel Disease

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

F

Family Communication

How family members share information, feelings, and decisions with each other, including which topics are open for discussion, who speaks for whom, and how disagreements are handled.

Example: A family meeting where Riya explains what a flare feels like and her grandmother asks how to help is open family communication.

See also: Caregiver Role

Taught in Chapter 19: Culture, Food, Family, and Stigma.

FDA Approval

The US Food and Drug Administration's decision, based on evidence a company submits, that a drug, biologic, or high-risk device is safe and effective for a specific intended use, meaning its benefits outweigh its risks for that use.

Example: Rebyota received FDA approval on November 30, 2022, to prevent recurrent C. difficile infection in adults, which is not approval for any other condition.

See also: Clinical Trial Phases, Off-Label Use

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Fecal Calprotectin

A protein released mainly by neutrophils that can be measured in stool. High levels signal inflammation in the intestines.

Example: A high fecal calprotectin result helps a doctor tell a Crohn's flare from IBS symptoms without inflammation.

See also: Disease Flare, Colonoscopy

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Fecal Microbiota Transplant

A procedure in which stool from a carefully screened healthy donor, containing that person's gut microbes, is delivered into a patient's digestive tract to restore a healthier microbial community. It is often shortened to FMT.

Example: A fecal microbiota transplant can be given through a colonoscope, an enema, a nasal tube, or capsules.

See also: C. difficile Infection, Live Biotherapeutic Product, Microbiota Transfer Therapy

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Fermentation

The process in which microbes break down carbohydrates without oxygen, releasing energy for themselves and leaving behind products such as gases and short-chain fatty acids.

Example: Bacteria in the colon carry out fermentation of the fiber in an apple, producing gas and short-chain fatty acids.

See also: Short-Chain Fatty Acid, Dietary Fiber

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

Fermented Food

Food made by letting microbes such as bacteria or yeasts transform it.

Example: Yogurt, kefir, kimchi, sauerkraut, miso, and idli and dosa batter are fermented foods.

See also: Probiotic, Fermentation

Taught in Chapter 15: Food and Mood.

Fight-or-Flight Response

The fast, nerve-driven part of the stress response, in which the sympathetic nervous system and the hormones epinephrine and norepinephrine prepare the body for sudden physical effort within seconds.

Example: A near-miss on a bike makes your heart race and your gut slow down within seconds through the fight-or-flight response.

See also: Sympathetic Nervous System, Stress Response

Taught in Chapter 7: Stress and the Gut.

FODMAP (Fermentable Oligo-, Di-, Monosaccharides and Polyols)

A type of short-chain carbohydrate that is poorly absorbed in the small intestine and quickly fermented by gut bacteria, which can draw water into the bowel and produce gas.

Example: Onions, garlic, wheat, and some fruits are high in FODMAPs.

See also: Low-FODMAP Diet, Fructan

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

Food Allergy

A harmful reaction caused by a specific immune response that happens reliably every time a person is exposed to a particular food.

Example: Hives and a swollen lip within 10 minutes of eating shrimp are signs of a food allergy.

See also: Immunoglobulin E, Food Intolerance

Taught in Chapter 12: Celiac Disease and Food Reactions.

Food Insecurity

The condition of not having reliable access to enough food for an active, healthy life because of limited money or other resources.

Example: In 2024, 13.7% of US households experienced food insecurity, according to the US Department of Agriculture.

See also: Dietary Pattern

Taught in Chapter 15: Food and Mood.

Food Intolerance

A reliable, unpleasant reaction to a food that does not involve the immune system, often because the body cannot fully digest something.

Example: Lactose intolerance is a food intolerance, not a food allergy.

See also: Lactose Intolerance, Food Allergy

Taught in Chapter 12: Celiac Disease and Food Reactions.

Free Fatty Acid Receptor

A protein on the surface of a cell that detects fatty acids outside the cell and passes a signal inside. Two of them, FFAR2 and FFAR3, respond to short-chain fatty acids.

Example: Short-chain fatty acids binding to free fatty acid receptors on enteroendocrine cells can trigger the release of gut hormones.

See also: Short-Chain Fatty Acid, Enteroendocrine Cell

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

Fructan

A carbohydrate built from linked fructose units that the human small intestine cannot break down. It is a type of FODMAP found in wheat and some other foods.

Example: Someone who feels better off wheat may be reacting to its fructans rather than its gluten.

See also: FODMAP (Fermentable Oligo-, Di-, Monosaccharides and Polyols), Non-Celiac Gluten Sensitivity

Taught in Chapter 12: Celiac Disease and Food Reactions.

Functional Dyspepsia

A disorder of gut-brain interaction of the upper gut, defined by bothersome fullness after meals, feeling full too early, or pain or burning in the upper belly, with no structural disease found to explain the symptoms.

Example: A person who feels painfully full after a few bites, with a normal upper endoscopy, may have functional dyspepsia.

See also: Gut-Brain Interaction Disorder

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

G

Gamma-Aminobutyric Acid (GABA)

The brain's main inhibitory neurotransmitter, which mostly makes receiving neurons less likely to fire, like a brake pedal.

Example: Some gut bacteria make GABA, but that does not show their GABA reaches or calms the brain.

See also: Microbe-Made Neurotransmitter, Neurotransmitter

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Gate Control Theory

The idea, proposed by Melzack and Wall in 1965, that the dorsal horn of the spinal cord works like a gate that can let pain signals through or partly block them, depending on other incoming signals and signals from the brain.

Example: Rubbing a bumped elbow eases the pain because touch signals help close the gate, as gate control theory predicts.

See also: Dorsal Horn, Descending Pain Modulation

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Gene Regulation by Butyrate

Butyrate's ability to block enzymes called histone deacetylases, which leaves more acetyl tags on histones and changes which genes a cell turns on.

Example: Gene regulation by butyrate is one of the three main ways short-chain fatty acids act, along with acting on receptors and serving as fuel.

See also: Butyrate, Regulatory T Cell

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

Germ-Free Mouse

A mouse raised in a sterile isolator from birth so that it has no microorganisms in or on its body, which lets researchers add specific microbes and watch what changes.

Example: Germ-free mice showed an exaggerated stress hormone response, and giving them one bacterial species, *Bifidobacterium infantis*, reversed it.

See also: Animal Model, Germ-Free Stress Response

Taught in Chapter 3: Meet the Microbiome.

Germ-Free Stress Response

The larger-than-normal HPA axis response to stress seen in mice raised without any microbes, which suggests that gut microbes help tune the stress system as it develops.

Example: Germ-free mice placed in a mildly stressful tube released more stress hormones than normal mice, an example of the germ-free stress response.

See also: Germ-Free Mouse, Hypothalamic-Pituitary-Adrenal (HPA) Axis

Taught in Chapter 7: Stress and the Gut.

GI Symptoms in Autism

The higher rate of digestive problems, such as constipation, diarrhea, and belly pain, reported in autistic children compared with non-autistic children. These are real health issues that deserve diagnosis and treatment, separate from autism itself.

Example: An autistic child who becomes irritable and stops sleeping well may be in pain from constipation, one of the common GI symptoms in autism.

See also: Selective Eating, Interoceptive Differences

Taught in Chapter 13: Autism, ADHD, and the Gut.

GI-Specific Anxiety

Worry and fear focused specifically on gut sensations, gut symptoms, or situations where they might happen, such as fearing a cramp in class or avoiding trips where a restroom is hard to reach.

Example: Researchers measure GI-specific anxiety with tools such as the 15-question Visceral Sensitivity Index.

See also: Anxiety Disorder, Interoception

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Global IBD Rise

The spread of inflammatory bowel disease from a few early industrialized regions to countries around the world over the last century, with rising new cases in many newly industrialized countries.

Example: A 2017 review of 147 studies found IBD incidence rising in newly industrialized countries in Asia, Africa, and South America.

See also: Migration and IBD Risk, IBD Risk Factors

Taught in Chapter 19: Culture, Food, Family, and Stigma.

Glucagon-Like Peptide-1 (GLP-1)

A gut hormone released after eating by L-cells in the intestinal lining that boosts insulin release when blood sugar is high, slows stomach emptying, and reduces food intake.

Example: Some diabetes and weight-loss medicines work by copying the action of GLP-1.

See also: Gut Hormone, Satiety Signal

Taught in Chapter 2: The Vagus Highway.

Gluten

A group of proteins found naturally in wheat, barley, and rye that gives bread dough its stretch.

Example: Gluten is found in bread and pasta, and also hides in processed foods that use malt or some starches.

See also: Celiac Disease, Non-Celiac Gluten Sensitivity

Taught in Chapter 12: Celiac Disease and Food Reactions.

Gluten Ataxia

A problem with balance and coordination linked to gluten sensitivity, thought to involve immune damage to the cerebellum, the part of the brain that fine-tunes movement.

Example: A person with celiac disease who becomes unsteady on their feet may be checked for gluten ataxia.

See also: Celiac Disease, Peripheral Neuropathy

Taught in Chapter 12: Celiac Disease and Food Reactions.

Gluten-Free Diet

An eating plan that strictly avoids wheat, barley, rye, and ingredients made from them. For people with celiac disease, it is lifelong and is the only proven treatment.

Example: On a gluten-free diet, symptoms often improve within weeks, but the villi can take much longer to grow back.

See also: Celiac Disease, Unneeded Restrictive Diet

Taught in Chapter 12: Celiac Disease and Food Reactions.

Gut Hormone

A chemical messenger made by cells of the digestive tract, mostly enteroendocrine cells, that travels through the blood or acts on nearby nerves to influence digestion, appetite, and blood sugar.

Example: Cholecystokinin and GLP-1 are two gut hormones that help you feel full.

See also: Cholecystokinin, Glucagon-Like Peptide-1 (GLP-1)

Taught in Chapter 2: The Vagus Highway.

Gut Microbiota

The community of living microorganisms in the digestive tract: the bacteria, archaea, fungi, and other microbes themselves.

Example: Most of your gut microbiota lives in the colon, where food moves slowly and there is little oxygen.

See also: Microbiome, Microbial Diversity

Taught in Chapter 3: Meet the Microbiome.

Gut Serotonin Mood Myth

The popular but unsupported claim that because most of the body's serotonin is made in the gut, the gut directly controls mood, so "healing your gut" will raise brain serotonin and make you happier.

Example: A post saying "95% of your happy chemical is in your gut, so fix your gut to fix your mood" repeats the gut serotonin mood myth.

See also: Serotonin, Blood-Brain Barrier

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Gut Wall Layers

The four tissue layers of the digestive tract wall, from the inside out: the mucosa (inner lining), the submucosa (connective tissue), the muscularis (muscle), and the serosa (thin outer covering).

Example: The submucosal plexus sits in the submucosa, while the myenteric plexus sits between the two muscle sheets of the muscularis.

See also: Digestive Tract, Myenteric Plexus, Submucosal Plexus

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Gut-Associated Lymphoid Tissue

The collection of immune tissue in the gut wall where immune cells sample what we swallow and organize responses, including the Peyer's patches, the appendix, and many small scattered clusters. It is often shortened to GALT.

Example: Peyer's patches in the ileum are part of the gut-associated lymphoid tissue.

See also: Adaptive Immunity, Regulatory T Cell

Taught in Chapter 4: The Immune System as a Sense Organ.

Gut-Brain Axis

The two-way communication system linking the gut (its nerves, hormones, immune cells, and microbes) with the brain. Signals travel through nerves, hormones, immune messengers, and microbial chemicals.

Example: Sam's belly cramping before a big test is one sign of the gut-brain axis carrying signals from brain to gut.

See also: Enteric Nervous System, Vagus Nerve, Bidirectional Relationship

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Gut-Brain Interaction Disorder

A condition in which gut symptoms come from problems in how the gut and brain communicate and process signals, such as increased gut sensitivity and altered gut movement, rather than from visible damage or inflammation. The plural is shortened to DGBI.

Example: Irritable bowel syndrome and functional dyspepsia are gut-brain interaction disorders.

See also: Irritable Bowel Syndrome, Structural vs Functional Disease

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

Gut-Brain Neuromodulator

A medicine that acts on the nervous system's processing of gut signals, often a low dose of a medicine first developed as an antidepressant, used to reduce gut pain and change gut movement in disorders of gut-brain interaction.

Example: A low-dose tricyclic antidepressant prescribed for IBS pain acts as a gut-brain neuromodulator, not as a treatment for depression.

See also: Tricyclic Antidepressant, Irritable Bowel Syndrome

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

Gut-Directed Hypnotherapy

A type of hypnotherapy in which a trained therapist guides a person into a deeply relaxed, focused state and uses suggestions and imagery aimed at calming the gut and changing how gut sensations are processed.

Example: Sam has been learning gut-directed relaxation, and gut-directed hypnotherapy is a structured, therapist-led version of that idea.

See also: Brain-Gut Psychotherapy, Cognitive Behavioral Therapy

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

Gut-First Subtype

A proposed form of Parkinson's disease in which alpha-synuclein pathology starts in the gut or other body nerves, reaches the brainstem through the vagus nerve, and climbs to the dopamine neurons later. It is also called "body-first."

Example: A person with years of constipation and dream-enactment before any tremor fits the predicted pattern of the gut-first subtype.

See also: Brain-First Subtype, Braak Hypothesis

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

H

Harmful Cure Claims

Promises that a product, diet, supplement, or procedure can cure or reverse autism or ADHD. They are unsupported by evidence and can cause harm through risky treatments, wasted money and time, missed care, and the message that neurodivergent people need fixing.

Example: A website promising that a supplement will "reverse autism" or "cure ADHD" is making harmful cure claims.

See also: Neurodiversity, Health Claim Marketing

Taught in Chapter 13: Autism, ADHD, and the Gut.

Health Claim Marketing

The use of health-related promises, such as "boosts immunity," "clinically proven," or "reduces stress," to sell products through labels, ads, websites, and influencer posts.

Example: An influencer post saying a gummy is "clinically proven to beat bloating" is health claim marketing.

See also: Structure-Function Claim, Conflict of Interest

Taught in Chapter 20: Be Your Own Scientist: Reading Health Claims.

Health Literacy

The ability to find, understand, and use health information and services to make decisions for yourself and others.

Example: Reading a medicine label and knowing when to call the doctor are parts of health literacy.

See also: Talking to Your Doctor, Science Communication

Taught in Chapter 19: Culture, Food, Family, and Stigma.

Healthy User Bias

A distortion in observational studies that happens because people who choose one health behavior often also have many other healthy habits and advantages, making that behavior look more beneficial than it really is.

Example: People who eat a lot of vegetables also tend to exercise more and smoke less, so healthy user bias can exaggerate the benefit of vegetables.

See also: Observational Study, Confounding Variable

Taught in Chapter 15: Food and Mood.

Heart Rate Variability

The natural variation in the time between one heartbeat and the next. Part of it reflects the vagus nerve braking the heart during each exhale. It is often shortened to HRV.

Example: Your heart speeds up slightly when you breathe in and slows when you breathe out, which shows up as heart rate variability.

See also: Vagal Tone, Slow Breathing

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Help-Seeking

The process of recognizing that you are struggling and reaching out for support, whether to a friend, family member, school counselor, doctor, or mental health professional.

Example: Telling a school counselor that worry about flares is keeping you from sleeping is an act of help-seeking.

See also: Help-Seeking Barriers, Crisis Resources

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Help-Seeking Barriers

The obstacles that keep people from getting care when they need it, including stigma, cost, not knowing where to go, long waits, language differences, and worries about privacy or what family and community will think.

Example: Not having a ride to appointments and fearing what relatives will say are help-seeking barriers.

See also: Help-Seeking, Mental Health Stigma

Taught in Chapter 19: Culture, Food, Family, and Stigma.

Hierarchy of Evidence

The idea that different kinds of studies give different levels of confidence about cause and effect, often drawn as a pyramid with the weakest kinds, such as anecdotes, at the bottom and the strongest, such as systematic reviews and meta-analyses, at the top.

Example: On the hierarchy of evidence, a well-done randomized controlled trial in people ranks above a single mouse study.

See also: Evidence Grade, Systematic Review

Taught in Chapter 20: Be Your Own Scientist: Reading Health Claims.

Hirschsprung Disease

A condition present from birth in which enteric neurons are missing from the last part of the large intestine, so that segment cannot relax and push stool forward, causing a blockage.

Example: A newborn who does not pass stool in the first days of life may be checked for Hirschsprung disease.

See also: Neural Crest, Enteric Nervous System

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

HLA-DQ2 and HLA-DQ8

Versions of immune-system genes in the human leukocyte antigen (HLA) family that make proteins on certain immune cells. Nearly everyone with celiac disease carries one or both.

Example: About 30% of people carry HLA-DQ2 or HLA-DQ8, but only about 3% of those carriers develop celiac disease.

See also: Celiac Disease

Taught in Chapter 12: Celiac Disease and Food Reactions.

Human Milk Oligosaccharides

A family of complex sugar molecules found in large amounts in human milk that the baby cannot digest, which instead feed certain helpful gut bacteria such as *Bifidobacterium*. They are often shortened to HMOs.

Example: Human milk oligosaccharides were first discovered as a "bifidus factor," food for helpful bacteria.

See also: Microbiome Development, Bifidobacterium, Prebiotic

Taught in Chapter 3: Meet the Microbiome.

Hype Meter

This book's four-level scale for grading how well the evidence supports a popular gut-brain claim: Strong, Moderate, Preliminary, or Hype.

Example: The claim that "70% of your immune system is in your gut" gets a Hype grade on the Hype Meter.

See also: Evidence Grade, Claim-Checking Method

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Hypothalamic-Pituitary-Adrenal (HPA) Axis

The hormone chain in which the hypothalamus signals the pituitary gland, the pituitary signals the adrenal glands, and the adrenal glands release cortisol.

Example: Before a big exam, Sam's HPA axis raises his cortisol level over minutes to hours.

See also: Corticotropin-Releasing Hormone, Adrenocorticotropic Hormone (ACTH), Cortisol

Taught in Chapter 7: Stress and the Gut.

Hypothalamus

A small region at the base of the brain that links the nervous system to the hormone system and helps control body temperature, hunger, thirst, sleep, and the stress response.

Example: During stress, the hypothalamus releases corticotropin-releasing hormone, starting the hormone chain that ends in cortisol.

See also: Pituitary Gland, Corticotropin-Releasing Hormone

Taught in Chapter 7: Stress and the Gut.

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IBD Risk Factors

The inherited and environmental factors that raise a person's chance of developing IBD without, on their own, causing it.

Example: Smoking is an IBD risk factor: research suggests it may double the chance of developing Crohn's disease.

See also: Inflammatory Bowel Disease, Migration and IBD Risk

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

IBD Surgery

An operation to remove a severely diseased section of bowel or to treat a complication of IBD, such as a stricture, fistula, abscess, severe bleeding, or precancerous changes.

Example: A person with Crohn's whose small intestine has a tight stricture may need IBD surgery to remove that segment.

See also: Crohn's Disease, Ulcerative Colitis

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

IBS Subtypes

Categories of IBS based on a person's main stool pattern on days with abnormal bowel movements: IBS with constipation, IBS with diarrhea, IBS with mixed bowel habits, and IBS that does not fit any of these.

Example: Sam has IBS with mixed bowel habits, one of the IBS subtypes.

See also: Irritable Bowel Syndrome

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

Identity-First Language

A way of describing a group that puts the identity first, such as "autistic person" instead of "person with autism," often preferred because many autistic people see autism as a core part of who they are.

Example: This book uses identity-first language for autism by default.

See also: Autism, Neurodiversity

Taught in Chapter 13: Autism, ADHD, and the Gut.

Illness Burden

The total load a health condition places on a person's life, including symptoms such as pain, urgency, and fatigue, plus missed school, appointments, side effects, costs, worry, and effects on friendships and self-image.

Example: Planning every outing around restrooms is part of the illness burden of a gut condition.

See also: Quality of Life, Psychiatric Comorbidity

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Illness Concealment

Keeping a health condition or its symptoms secret from others, such as by making up excuses for missed school or not telling a doctor about embarrassing symptoms.

Example: Skipping lunch to avoid bathroom trips so no one finds out about your IBS is illness concealment.

See also: Self-Stigma, Talking to Your Doctor

Taught in Chapter 19: Culture, Food, Family, and Stigma.

Immune-Mediated Disease

A condition in which the body's own immune response, rather than an outside germ or a toxin, causes most of the damage.

Example: Inflammatory bowel disease, rheumatoid arthritis, and psoriasis are immune-mediated diseases.

See also: Inflammatory Bowel Disease, Regulatory T Cell

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Immune-to-Brain Signaling

The set of pathways by which messages from the immune system, especially cytokines, reach the brain and change its activity, such as through the vagus nerve and leaky spots in the blood-brain barrier.

Example: Cytokines from a gut infection activating vagal sensory fibers is one route of immune-to-brain signaling.

See also: Circumventricular Organ, Sickness Behavior

Taught in Chapter 4: The Immune System as a Sense Organ.

Immunoglobulin E

A class of antibody that drives immediate allergic reactions. In food allergy, it sits on immune cells such as mast cells and triggers them to release chemicals within minutes when the food is eaten. It is often shortened to IgE.

Example: Immunoglobulin E against a food protein, sitting on mast cells, is why an allergic reaction can start within minutes of eating.

See also: Food Allergy, Mast Cell

Taught in Chapter 12: Celiac Disease and Food Reactions.

Immunomodulator

A medicine that dampens the immune system's activity more slowly and steadily, used mainly to maintain remission or help other medicines work better.

Example: Azathioprine is an immunomodulator that can take weeks to months to work fully.

See also: Corticosteroid, Biologic Therapy

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Implanted VNS Device

A small pulse generator placed under the skin by a surgeon and connected to the vagus nerve in the neck, which delivers programmed electrical pulses on a schedule.

Example: Implanted VNS devices are FDA approved for drug-resistant partial-onset epilepsy (1997), treatment-resistant depression in adults (2005), with the Vivistim System, arm-movement rehabilitation after stroke (2021), and, with the SetPoint System, moderate to severe rheumatoid arthritis in adults (July 30, 2025).

See also: Vagus Nerve Stimulation, Bioelectronic Medicine

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Inflammation

The body's protective response to infection or injury, in which blood vessels widen and leak, immune cells rush in, and the area becomes warm, red, swollen, and painful.

Example: A scraped knee that turns red and puffy is showing inflammation.

See also: Cytokine, Neuroinflammation

Taught in Chapter 4: The Immune System as a Sense Organ.

Inflammatory Bowel Disease

A group of chronic conditions in which abnormal immune reactions cause long-lasting, recurring inflammation of the digestive tract. Its two main forms are ulcerative colitis and Crohn's disease. It is often shortened to IBD.

Example: In US claims data, about 721 per 100,000 people, roughly 2.39 million Americans, have inflammatory bowel disease.

See also: Ulcerative Colitis, Crohn's Disease, Immune-Mediated Disease

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Inflammatory Depression Theory

The idea that ongoing inflammation in the body, signaled to the brain by cytokines and other immune messengers, can push brain circuits toward depression-like changes in mood, energy, and motivation, at least in some people.

Example: Higher depression symptom rates during active IBD than in remission fit, but do not prove, the inflammatory depression theory.

See also: Sickness Behavior, Cytokine

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Inflammatory Reflex

A nerve circuit in which the brain senses inflammation, partly through incoming vagus signals, and responds by sending signals back out, largely through the vagus nerve, that calm the immune system's release of inflammatory chemicals such as cytokines.

Example: The SetPoint System for rheumatoid arthritis is designed to use the inflammatory reflex by stimulating the vagus nerve.

See also: Vagus Nerve Stimulation, Cytokine

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Innate Immunity

The fast, general part of the immune system present from birth that responds within minutes to hours to broad signs of trouble and reacts the same way each time.

Example: Macrophages swallowing bacteria that slip past the gut lining are part of innate immunity.

See also: Adaptive Immunity, Pattern Recognition Receptor

Taught in Chapter 4: The Immune System as a Sense Organ.

Insula

A region of cortex folded deep inside each side of the brain that maps signals from inside the body, such as gut stretch, heartbeat, and breathing. It is a key area for interoception.

Example: In brain scans, gut stretch from a balloon consistently activated the thalamus, the insula, and part of the cingulate cortex.

See also: Interoception, Anterior Cingulate Cortex

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Integrated Care

An approach in which physical and mental health care are delivered together by a coordinated team, such as a gastroenterologist, nurse, dietitian, and psychologist who share information and plan care as one team.

Example: A clinic where an IBD patient sees the gastroenterologist and the psychologist in the same visit is offering integrated care.

See also: Psychiatric Comorbidity, Brain-Gut Psychotherapy

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Interleukin-1 Beta

A pro-inflammatory cytokine released by activated innate immune cells, such as macrophages, early in an immune response. It helps coordinate local and body-wide inflammation and is strongly linked to sickness behavior.

Example: Interleukin-1 beta released during the flu is one reason you feel tired and lose your appetite.

See also: Cytokine, Sickness Behavior

Taught in Chapter 4: The Immune System as a Sense Organ.

Interleukin-6

A pro-inflammatory cytokine released during inflammation that travels in the blood and helps produce body-wide effects such as fever and the liver's acute phase response. It is often shortened to IL-6.

Example: Because it is easy to measure in blood, interleukin-6 appears in many human studies of inflammation and mood.

See also: Cytokine, Inflammatory Depression Theory

Taught in Chapter 4: The Immune System as a Sense Organ.

Interoception

The process by which the nervous system senses, interprets, and combines signals from inside the body, such as fullness, nausea, heartbeat, and breathing, building a moment-to-moment map of the body's internal state.

Example: Noticing that your heart is pounding and your stomach is fluttering before a speech is interoception.

See also: Interoceptive Differences, Insula

Taught in Chapter 2: The Vagus Highway.

Interoceptive Differences

Differences in how a person notices, interprets, or reports signals from inside the body, such as hunger, pain, or the need to use the bathroom.

Example: A child with interoceptive differences may not notice they need the bathroom until it is urgent.

See also: Interoception, GI Symptoms in Autism

Taught in Chapter 13: Autism, ADHD, and the Gut.

Interstitial Cells of Cajal

Specialized cells in the gut's muscle layers that generate rhythmic electrical signals, called slow waves, which set the timing of smooth muscle contractions. They are neither neurons nor muscle cells.

Example: Interstitial cells of Cajal act like a pacemaker, setting the beat that the gut's smooth muscle contracts to.

See also: Smooth Muscle, Peristalsis

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Intestinal Epithelium

The single layer of cells that lines the inside of the intestine and forms the barrier between the gut's contents and the body.

Example: Most cells of the intestinal epithelium absorb nutrients, while goblet cells in the same layer make mucus.

See also: Mucus Layer, Tight Junction

Taught in Chapter 4: The Immune System as a Sense Organ.

Intestinal Permeability

How easily substances pass across the gut lining from inside the intestine into the body, either through the cells or through the gaps between them. Some permeability is normal and necessary.

Example: Endurance exercise and common pain relievers such as ibuprofen can raise intestinal permeability for a while.

See also: Tight Junction, Leaky Gut Claim

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

Intestinal Villi

Tiny, finger-like projections of the small intestine's lining that greatly increase its surface area for absorbing nutrients.

Example: Each of the intestinal villi is only about 0.5 to 1 millimeter long.

See also: Villous Atrophy, Small Bowel Biopsy

Taught in Chapter 12: Celiac Disease and Food Reactions.

Irritable Bowel Syndrome

A common disorder of gut-brain interaction marked by recurring belly pain linked to bowel movements and changes in how often stool happens or how it looks, without visible damage or disease in the digestive tract. It is often shortened to IBS.

Example: By Rome IV criteria, 6.1% of US adults had irritable bowel syndrome in a 2020 online survey.

See also: Rome IV Criteria, IBS Subtypes, Visceral Hypersensitivity

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

J

JAK Inhibitor

A pill, a small molecule rather than an antibody, that blocks Janus kinase (JAK) enzymes inside immune cells, which relay signals from many cytokines at once.

Example: Tofacitinib and upadacitinib are JAK inhibitors used for some people with IBD.

See also: Biologic Therapy, Cytokine

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

K

Kynurenine Pathway

The main chemical route for breaking down tryptophan, mostly in the liver, producing kynurenine and a series of other products, some of which can act on brain cells.

Example: More than 95% of dietary tryptophan is broken down through the kynurenine pathway, and only a small part becomes serotonin.

See also: Tryptophan, Inflammatory Depression Theory

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

L

Lactobacillus

A group of bacteria known for turning sugars into lactic acid, used to make yogurt and other fermented foods. In 2020 the old genus was split into 25 genera, so many species now have new names.

Example: The species once called *Lactobacillus rhamnosus* is now named *Lacticaseibacillus rhamnosus*.

See also: Bifidobacterium, Bacterial Strain

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Lactose Intolerance

Digestive symptoms such as bloating, gas, and diarrhea after eating or drinking lactose (milk sugar), because the small intestine makes too little of the enzyme lactase to break it all down.

Example: A teen with lactose intolerance may have bloating, gas, and diarrhea for an afternoon after drinking a milkshake.

See also: Food Intolerance

Taught in Chapter 12: Celiac Disease and Food Reactions.

Leaky Gut Claim

The popular idea that "leaky gut syndrome" is a common hidden cause of many symptoms and diseases and can be diagnosed with consumer tests and cured with diets or supplements. "Leaky gut syndrome" is not a recognized medical diagnosis.

Example: An ad selling a supplement to "seal your leaky gut and cure your fatigue" is making the leaky gut claim.

See also: Intestinal Permeability, Hype Meter

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

Levodopa Absorption

The process by which levodopa taken by mouth passes from the gut into the bloodstream. In Parkinson's it can be delayed or uneven because of slow stomach emptying, constipation, and competition from protein in meals.

Example: Delayed stomach emptying in Parkinson's can slow levodopa absorption and lead to more "off" periods, when symptoms come back.

See also: Parkinson's Disease, Constipation

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Lewy Body

An abnormal round clump, made mostly of misfolded alpha-synuclein, found inside nerve cells in Parkinson's disease and some related conditions.

Example: At autopsy, pathologists see Lewy bodies in the damaged brain cells of most people who had Parkinson's.

See also: Alpha-Synuclein, Parkinson's Disease

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Lipopolysaccharide

A large molecule made of fat and sugar parts that forms much of the outer membrane of gram-negative bacteria. Immune cells detect it through pattern recognition receptors and respond with inflammation. It is also called endotoxin, or LPS.

Example: In a serious infection, large amounts of lipopolysaccharide in the blood can trigger a dangerous body-wide reaction.

See also: Metabolic Endotoxemia, Pattern Recognition Receptor

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

Live Biotherapeutic Product

A medicine that contains live microorganisms and is meant to prevent, treat, or cure a disease, reviewed by the FDA like other drugs rather than sold as a supplement. It is often shortened to LBP.

Example: Vowst, oral capsules approved April 26, 2023, is a live biotherapeutic product used to prevent C. difficile infection from coming back in adults.

See also: Fecal Microbiota Transplant, FDA Approval, Probiotic

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Low-FODMAP Diet

A structured, short-term eating plan, best done with a dietitian, in which a person cuts back on high-FODMAP foods for a few weeks and then adds them back one group at a time to find triggers, so the long-term diet can stay as broad as possible.

Example: Working with a dietitian, a teen with IBS on a low-FODMAP diet finds that onions trigger symptoms but wheat does not.

See also: FODMAP (Fermentable Oligo-, Di-, Monosaccharides and Polyols), Unneeded Restrictive Diet

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

M

Major Depressive Disorder

A mental health condition marked by at least two weeks of depressed mood or loss of interest or pleasure in daily activities, along with other symptoms such as changes in sleep, appetite, energy, concentration, or self-worth. It is often just called depression.

Example: A teen who has felt hopeless, lost interest in friends, and slept poorly for most of a month should be checked for major depressive disorder.

See also: Anxiety Disorder, Inflammatory Depression Theory

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Mast Cell

An immune cell that lives in tissues, including the gut lining, and stores chemical signals such as histamine and tryptase that it can release quickly, causing inflammation, changing nerve signaling, and loosening the barrier.

Example: Stress signals can activate mast cells in the gut wall, which then irritate nearby nerve endings.

See also: Immunoglobulin E, Visceral Hypersensitivity

Taught in Chapter 7: Stress and the Gut.

Maternal Immune Activation

A strong immune response in a pregnant animal or person, such as from an infection. In research, it is usually triggered on purpose in pregnant mice to study effects on the offspring. It is often shortened to MIA.

Example: Offspring of mice exposed to maternal immune activation showed behaviors researchers label "autism-like," a mouse finding that does not show the same happens in people.

See also: Animal Model, Mouse-to-Human Translation

Taught in Chapter 13: Autism, ADHD, and the Gut.

Mediator Variable

A factor that lies on the causal path between a cause and an outcome and helps explain how the cause produces its effect.

Example: If fiber improved mood by changing gut microbes, the microbes would be a mediator variable.

See also: Confounding Variable

Taught in Chapter 15: Food and Mood.

Mediterranean Diet

A dietary pattern based on traditional eating habits of countries around the Mediterranean Sea, rich in vegetables, fruits, whole grains, legumes, nuts, olive oil, and fish, with fewer highly processed foods.

Example: In the SMILES trial, dietitians coached people toward a Mediterranean-style diet built from 12 food groups.

See also: Dietary Pattern, SMILES Trial

Taught in Chapter 15: Food and Mood.

Mental Health Stigma

Stigma directed at people with mental health conditions or at the act of seeking mental health care.

Example: Believing that seeing a therapist means you are "crazy" is mental health stigma.

See also: Stigma, Help-Seeking Barriers

Taught in Chapter 19: Culture, Food, Family, and Stigma.

Meta-Analysis

A study that uses statistics to combine the results of many earlier studies on the same question into a single pooled estimate, usually more reliable than any one study, but only as good as the studies it includes.

Example: The estimate that 39.1% of people with IBS have anxiety symptoms comes from a meta-analysis.

See also: Systematic Review, Publication Bias

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Metabolic Endotoxemia

A small, long-lasting increase in blood lipopolysaccharide, linked to diet and gut microbes, that may promote low-grade inflammation and metabolic problems such as insulin resistance.

Example: Mice fed a high-fat diet developed metabolic endotoxemia, with a low but chronic rise in blood LPS.

See also: Lipopolysaccharide, Inflammation

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

Metagenomic Sequencing

A method that reads fragments of all the DNA in a sample, from every organism present, so researchers can identify microbes in more detail and see which genes, and so which possible functions, are present. It is also called shotgun metagenomics.

Example: Metagenomic sequencing of a stool sample can show whether the community carries genes for making butyrate.

See also: 16S rRNA Sequencing, Microbiome

Taught in Chapter 3: Meet the Microbiome.

Microbe-Made Neurotransmitter

A chemical produced by bacteria or other microbes that is the same molecule the human body uses as a neurotransmitter, such as GABA, dopamine, or serotonin.

Example: A gut bacterium that produces GABA in a lab dish is making a microbe-made neurotransmitter, though that alone does not show an effect on the brain.

See also: Gamma-Aminobutyric Acid (GABA), Blood-Brain Barrier

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Microbial Diversity

A measure of how many different kinds of microbes live in a community (richness) and how evenly their numbers are spread (evenness).

Example: A gut community with 300 kinds of bacteria in balanced numbers has higher microbial diversity than one dominated by a single kind.

See also: Dysbiosis, Defining a Healthy Microbiome

Taught in Chapter 3: Meet the Microbiome.

Microbiome

The gut microbiota plus its "theater of activity": the microbes' genes, the molecules they make, and the environment they live in. In everyday talk, the word often means just the microbes.

Example: When researchers study which vitamins gut bacteria can make, they are studying the microbiome, not just a list of species.

See also: Gut Microbiota, Metagenomic Sequencing

Taught in Chapter 3: Meet the Microbiome.

Microbiome Daily Rhythm

The repeating, roughly 24-hour change in which gut microbes are most abundant, where they sit in the gut, and what chemicals they make, shaped largely by when the host eats.

Example: A 2014 study found that gut bacteria in mice and people rise and fall over the day, driven largely by feeding rhythms, showing a microbiome daily rhythm.

See also: Circadian Rhythm, Microbiome

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Microbiome Development

The process by which a newborn's gut, which starts with very few microbes, is colonized and changes over the first years of life toward a more stable, adult-like community.

Example: Like a cleared field where pioneer plants arrive first, microbiome development starts with a few fast-growing microbes and becomes richer over time.

See also: Birth Mode and Microbes, Human Milk Oligosaccharides

Taught in Chapter 3: Meet the Microbiome.

Microbiota Transfer Study

An experiment in which gut microbes, usually from stool, from one group of people or animals are moved into animals whose own gut microbes have been removed or depleted, to see whether traits move along with the microbes.

Example: In a microbiota transfer study, rats given gut microbes from people with depression showed behaviors researchers read as depression-like.

See also: Germ-Free Mouse, Microbiota Transfer Therapy

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Microbiota Transfer Therapy

An experimental treatment protocol in which a person receives antibiotics, a bowel cleanse, and stomach-acid medicine, followed by repeated doses of processed stool from healthy donors to try to replace their gut microbes. It is often shortened to MTT.

Example: The 2017 Kang study of microbiota transfer therapy in 18 autistic children aged 7 to 16 was open-label with no placebo group, so it does not prove a treatment.

See also: Fecal Microbiota Transplant, Open-Label Trial

Taught in Chapter 13: Autism, ADHD, and the Gut.

Microglia

The brain's resident immune cells, a type of macrophage that lives permanently in the brain and spinal cord, surveying its surroundings, clearing debris, pruning connections, and responding to injury or infection.

Example: When an infection signals the brain, microglia switch to an active state and release cytokines.

See also: Neuroinflammation, Microglia Maturation

Taught in Chapter 4: The Immune System as a Sense Organ.

Microglia Maturation

The process by which young microglia develop into fully functional immune cells that can watch over brain tissue and respond to infection or injury.

Example: Germ-free mice had immature microglia, and giving them a mixture of acetate, propionate, and butyrate drove microglia maturation forward.

See also: Microglia, Germ-Free Mouse

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

Microorganism

A living thing too small to see without a microscope, such as a bacterium, an archaeon, a yeast, or a single-celled parasite. It is also called a microbe.

Example: The yeast that makes bread rise is a microorganism.

See also: Gut Microbiota, Pathogen

Taught in Chapter 3: Meet the Microbiome.

Migrating Motor Complex

A repeating pattern of strong contractions that sweeps slowly along the stomach and small intestine during fasting, between meals. It is often shortened to MMC.

Example: Like a street sweeper on a schedule, the migrating motor complex clears leftover debris toward the large intestine overnight.

See also: Peristalsis

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Migration and IBD Risk

How the risk of developing IBD changes when people move from one country or environment to another, and what those changes suggest about the roles of genes and environment.

Example: In Leicestershire, England, South Asians had a higher relative risk of ulcerative colitis than Europeans in a 1992 study, a classic finding on migration and IBD risk.

See also: Global IBD Rise, South Asian Health Context

Taught in Chapter 19: Culture, Food, Family, and Stigma.

Mindfulness

The practice of paying attention to the present moment, including thoughts and body sensations, on purpose and without judging them.

Example: Noticing a cramp as "tightness, lower left, about a 4 out of 10" instead of spiraling into worry is mindfulness.

See also: Slow Breathing, Pain Catastrophizing

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Mouse-to-Human Translation

The process of testing whether a finding in mice or other animals holds true in people, along with the frequent failure of animal results to carry over.

Example: About one in three highly cited animal studies were later confirmed in human trials, showing how often mouse-to-human translation fails.

See also: Animal Model, Replication Failure

Taught in Chapter 20: Be Your Own Scientist: Reading Health Claims.

Mucosal Healing

Healing of the gut's inner lining, so that ulcers and visible inflammation are gone when doctors look with an endoscope. It is also called endoscopic healing.

Example: Even though Riya feels well, her doctor checks for mucosal healing because hidden inflammation can damage the bowel over time.

See also: Remission, Colonoscopy

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Mucus Layer

The slippery gel, made mostly of large proteins called mucins, that coats the intestinal epithelium and keeps most microbes at a distance.

Example: In mice, the colon's mucus layer has a dense inner part that bacteria cannot enter and a looser outer part where they live.

See also: Intestinal Epithelium, Tight Junction

Taught in Chapter 4: The Immune System as a Sense Organ.

Myenteric Plexus

The outer network of enteric ganglia, lying between the circular and longitudinal muscle layers along the whole gut, that mainly controls the rhythm and strength of gut contractions. It is also called Auerbach's plexus.

Example: When the myenteric plexus signals the muscle behind a lump of food to squeeze, the food moves forward.

See also: Submucosal Plexus, Peristalsis

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

N

Negative Feedback

A control loop in which the product of a process acts back on the process to slow or stop it, keeping a body system near a set level.

Example: Rising cortisol tells the hypothalamus and pituitary to release less CRH and ACTH, a classic case of negative feedback.

See also: Cortisol, Hypothalamic-Pituitary-Adrenal (HPA) Axis

Taught in Chapter 7: Stress and the Gut.

Neural Crest

A group of embryonic cells that forms at the edge of the developing neural tube and migrates through the embryo, giving rise to many cell types, including the neurons and glia of the enteric nervous system.

Example: If neural crest cells stop migrating before they reach the end of the colon, that segment has no enteric neurons.

See also: Hirschsprung Disease, Enteric Nervous System

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Neurodegeneration

The slow, progressive loss of the structure and function of neurons, ending in their death, in particular parts of the nervous system.

Example: Parkinson's disease and Alzheimer's disease are the two most common diseases of neurodegeneration.

See also: Parkinson's Disease, Alzheimer's Disease

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Neurodiversity

The idea that natural variation in how human brains develop and work, including autism and ADHD, is part of normal human diversity, so the goal is understanding, support, and accommodation rather than cure.

Example: Like left-handedness, which was once treated as a defect, neurodiversity treats brain differences as differences that need the right tools.

See also: Autism, Identity-First Language

Taught in Chapter 13: Autism, ADHD, and the Gut.

Neuroinflammation

Inflammation within the brain or spinal cord, involving activated microglia and other glia releasing cytokines and other inflammatory chemicals. It ranges from a brief, helpful response to a long-lasting state.

Example: Multiple sclerosis involves long-lasting neuroinflammation.

See also: Microglia, Inflammation

Taught in Chapter 4: The Immune System as a Sense Organ.

Neuropod Cell

An enteroendocrine cell that forms synapse-like connections with nerve fibers and signals to them quickly, so far described mostly in mice.

Example: In lab dishes, vagal neurons connected to neuropod cells responded to gut nutrients within milliseconds.

See also: Enteroendocrine Cell, Synapse

Taught in Chapter 2: The Vagus Highway.

Neurotransmitter

A chemical messenger that a neuron releases at a synapse, which crosses the gap and binds to receptors on the receiving cell, making it more or less likely to fire or changing how it works.

Example: Acetylcholine is the neurotransmitter the vagus nerve releases onto its targets.

See also: Synapse, Serotonin, Dopamine

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Nociceptor

A sensory nerve ending that responds to stimuli that could damage tissue, such as strong pressure, extreme heat, harsh chemicals, or chemicals released during inflammation. Nociceptors detect possible harm; they are not the same as pain.

Example: Nociceptors in your fingertip fire when you touch a hot pan.

See also: Pain Perception, Peripheral Sensitization

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Nodose Ganglion

The cluster of cell bodies of vagal sensory neurons, located on the vagus nerve just below the skull. It is also called the inferior vagal ganglion.

Example: A stretch signal from the stomach passes through a neuron in the nodose ganglion on its way to the brainstem.

See also: Vagus Nerve, Nucleus Tractus Solitarius

Taught in Chapter 2: The Vagus Highway.

Non-Celiac Gluten Sensitivity

A condition in which people without celiac disease or wheat allergy report gut or other symptoms after eating gluten-containing foods that improve when they avoid them. It does not damage the villi and has no biomarker.

Example: A person with negative celiac tests who still feels bloated after bread may be evaluated for non-celiac gluten sensitivity, though fructans may be the real trigger.

See also: Celiac Disease, Fructan

Taught in Chapter 12: Celiac Disease and Food Reactions.

Noninvasive VNS

Vagus nerve stimulation delivered through the skin, without surgery, using a handheld or wearable device placed on the neck or ear.

Example: gammaCore, a handheld noninvasive VNS device, is FDA authorized for cluster headache (2017) and migraine (2018) in adults.

See also: Vagus Nerve Stimulation, Consumer Wellness Device

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Nucleus Tractus Solitarius

A cluster of neurons in the medulla that receives incoming sensory signals from the vagus nerve and passes them on to other brain areas. It is also called the nucleus of the solitary tract (NTS).

Example: Fullness signals from the gut reach the nucleus tractus solitarius before being relayed to areas that control appetite.

See also: Nodose Ganglion, Brainstem

Taught in Chapter 2: The Vagus Highway.

Nutritional Psychiatry

The young research field that studies how diet and nutrition relate to mental health, including whether changing diet can help prevent or treat conditions like depression and anxiety.

Example: The SMILES trial is a key study in nutritional psychiatry.

See also: SMILES Trial, Dietary Pattern

Taught in Chapter 15: Food and Mood.

O

Observational Study

A study in which researchers measure what people already do and their health, without assigning anyone to change anything, and then look for links.

Example: A study that surveys thousands of people about their diets and moods is an observational study.

See also: Randomized Controlled Trial, Healthy User Bias

Taught in Chapter 15: Food and Mood.

Off-Label Use

The use of an FDA-approved drug for a condition, dose, or form that is not listed in its official labeling.

Example: Prescribing a low-dose antidepressant for gut pain in IBS is an example of off-label use.

See also: FDA Approval, Tricyclic Antidepressant

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Open-Label Trial

A study in which participants, families, and researchers all know who is getting the treatment. There is usually no placebo group, so improvements may come from expectations, extra attention, or time passing.

Example: The 2017 microbiota transfer study in 18 autistic children was an open-label trial with no placebo group.

See also: Placebo-Controlled Trial, Placebo Response

Taught in Chapter 13: Autism, ADHD, and the Gut.

P

Pain Catastrophizing

A pattern of thinking about pain in which a person tends to dwell on it, expect the worst from it, and feel helpless to do anything about it.

Example: Thinking "this cramp means something terrible is happening and I can't do anything" is an example of pain catastrophizing.

See also: Pain Perception, Cognitive Behavioral Therapy

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Pain Perception

The brain's construction of the conscious experience of pain from incoming nerve signals, shaped by attention, emotion, memory, and context. It is separate from nociception, the nerve activity caused by a harmful stimulus.

Example: The same cramp can feel worse during a stressful test than during a fun movie because pain perception depends on context.

See also: Nociceptor, Descending Pain Modulation

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Parasympathetic Nervous System

The branch of the autonomic nervous system that supports "rest and digest" activities, such as slowing the heart and speeding up digestion. Its nerves leave from the brainstem and the lowest part of the spinal cord.

Example: After a calm meal, the parasympathetic nervous system, mainly through the vagus nerve, helps the stomach and intestines get to work.

See also: Sympathetic Nervous System, Vagus Nerve

Taught in Chapter 2: The Vagus Highway.

Parkinson's Disease

A progressive disorder of the nervous system that mainly affects movement, caused by the gradual damage and death of nerve cells in certain parts of the brain. It is often shortened to PD.

Example: Tremor, rigidity, slowness of movement, and balance problems are the four common movement symptoms of Parkinson's disease.

See also: Dopamine Neuron Loss, Alpha-Synuclein, Braak Hypothesis

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Pathogen

A microorganism that can cause disease. Some cause disease in almost anyone; others, called opportunists, cause trouble mainly when the normal community or the body's defenses are weakened.

Example: *Clostridioides difficile* is an opportunistic pathogen that often takes hold after antibiotics.

See also: Commensal Bacteria, Colonization Resistance

Taught in Chapter 3: Meet the Microbiome.

Pattern Recognition Receptor

A protein on or inside an immune cell (and some other cells, such as gut lining cells) that recognizes molecular patterns shared by many microbes, or molecules released by stressed or damaged cells. It is often shortened to PRR.

Example: A pattern recognition receptor on a macrophage detects lipopolysaccharide from bacterial walls and starts inflammation.

See also: Innate Immunity, Lipopolysaccharide

Taught in Chapter 4: The Immune System as a Sense Organ.

Pediatric IBD

Inflammatory bowel disease that begins in childhood or the teen years, before adulthood. It can slow growth, lower weight gain, and delay puberty.

Example: Riya, diagnosed with Crohn's at 14, has pediatric IBD.

See also: Inflammatory Bowel Disease, School Accommodation

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Peer Review

The process in which a journal sends a submitted paper to independent experts in the same field, who check its methods, reasoning, and conclusions and recommend whether it should be published, revised, or rejected.

Example: Like a building inspector, peer review catches many problems but cannot check every detail of a study.

See also: Preprint

Taught in Chapter 20: Be Your Own Scientist: Reading Health Claims.

Peer Support

Help and understanding from people who share a similar experience, offered through friendships, support groups, online communities, or camps.

Example: Camp Oasis, a summer camp for kids and teens with IBD, offers peer support.

See also: Stigma, Help-Seeking

Taught in Chapter 19: Culture, Food, Family, and Stigma.

Peppermint Oil

An oil from the peppermint plant, usually taken in coated capsules that release it in the intestine, that relaxes gut smooth muscle and is used to ease IBS symptoms such as pain and cramping.

Example: A meta-analysis of 10 randomized trials found peppermint oil did better than placebo for overall IBS symptoms.

See also: Irritable Bowel Syndrome, Smooth Muscle

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

Peripheral Nervous System

All the nerves and nerve-cell clusters (ganglia) outside the brain and spinal cord, which connect the central nervous system to the skin, muscles, and organs. It is often shortened to PNS.

Example: The vagus nerve running from the brainstem to the gut is part of the peripheral nervous system.

See also: Central Nervous System, Autonomic Nervous System

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Peripheral Neuropathy

Damage to the nerves outside the brain and spinal cord, often causing numbness, tingling, burning, or weakness, usually starting in the hands and feet.

Example: Tingling feet in a person with untreated celiac disease may be a sign of peripheral neuropathy.

See also: Gluten Ataxia, Peripheral Nervous System

Taught in Chapter 12: Celiac Disease and Food Reactions.

Peripheral Sensitization

An increase in how strongly sensory nerve endings in a tissue respond, with a drop in the stimulus needed to make them fire, usually caused by inflammation or injury in that tissue.

Example: Inflammation in the gut wall can make its nerve endings fire at a gentler stretch than usual, a form of peripheral sensitization.

See also: Central Sensitization, Nociceptor

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Peristalsis

A wave of muscle contraction that travels along the digestive tract and pushes its contents forward, toward the anus.

Example: Peristalsis is why food still reaches your stomach if you swallow while lying down.

See also: Peristaltic Reflex, Migrating Motor Complex

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Peristaltic Reflex

A local reflex of the enteric nervous system in which stretch of the gut wall makes the muscle behind the stretched spot contract and the muscle ahead of it relax.

Example: A lump of food stretches the intestine, so the muscle above it squeezes and the muscle below it relaxes, moving the lump along.

See also: Peristalsis, Enteric Nervous System

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Physical Activity

Any body movement produced by skeletal muscles that uses energy. Exercise is the planned, repeated kind.

Example: The CDC says children and teens ages 6 to 17 should get 60 minutes or more of moderate-to-vigorous physical activity every day.

See also: Exercise and Gut Transit, Exercise and Mood

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Pituitary Gland

A pea-sized gland hanging just below the hypothalamus that releases hormones controlling many other glands. Its front part, the anterior pituitary, releases ACTH in the stress response.

Example: The pituitary gland responds to corticotropin-releasing hormone by releasing ACTH into the blood.

See also: Hypothalamus, Adrenocorticotropic Hormone (ACTH)

Taught in Chapter 7: Stress and the Gut.

Placebo Response

The improvement in symptoms people experience after receiving an inactive treatment, caused by expectations, attention and care, natural ups and downs of symptoms, and changes in how the brain processes body signals.

Example: In IBS trials, many people in the placebo group report feeling better, which is the placebo response, not faking.

See also: Placebo-Controlled Trial, Open-Label Trial

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

Placebo-Controlled Trial

A study that compares a real treatment with a look-alike dummy treatment, ideally with assignment by chance and with neither participants nor researchers knowing who got which (double-blind), so expectation effects are the same in both groups.

Example: A placebo-controlled trial of a probiotic gives half the group identical-looking empty capsules.

See also: Open-Label Trial, Randomized Controlled Trial

Taught in Chapter 13: Autism, ADHD, and the Gut.

Polyphenol

One of a large family of natural chemical compounds made by plants that may affect the body partly through the gut microbes that break them down.

Example: Berries, grapes, tea, and turmeric contain polyphenols, and most of the polyphenols people eat reach the large intestine.

See also: Gut Microbiota

Taught in Chapter 15: Food and Mood.

Positive Diagnosis Strategy

An approach in which a clinician diagnoses IBS confidently from its typical symptom pattern, a careful history and exam, the absence of alarm features, and a few targeted tests, instead of first ordering every possible test.

Example: Using a positive diagnosis strategy, a doctor diagnoses IBS with diarrhea from the typical symptom pattern plus a celiac blood test and a fecal calprotectin test, without a long list of scans.

See also: Rome IV Criteria, Alarm Features

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

Post-Infection IBS

IBS that develops after a bout of infectious gastroenteritis, such as food poisoning, in a person who did not have IBS before.

Example: In a meta-analysis of 45 studies, about 10.1% of people had IBS 12 months after infectious enteritis, an example of post-infection IBS.

See also: Irritable Bowel Syndrome

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

Postbiotic

A preparation of inanimate (no longer alive) microorganisms and/or their components that confers a health benefit on the host (ISAPP, 2021).

Example: Heat-killed bacterial cells with a shown health benefit can be a postbiotic, but a purified chemical made by microbes, on its own, does not count.

See also: Probiotic, Synbiotic

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Prebiotic

A substrate that is selectively utilized by host microorganisms conferring a health benefit (ISAPP, 2017). In plain words, food that feeds certain microbes more than others and produces a health benefit.

Example: Many prebiotics are types of fiber that certain gut bacteria ferment more readily than others.

See also: Probiotic, Synbiotic, Dietary Fiber

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Precision Medicine

An emerging approach to disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person, instead of a one-size-fits-all approach.

Example: Choosing an IBS treatment someday based on a person's microbiome or genes would be precision medicine.

See also: Shared Decision-Making

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Preprint

A complete scientific paper shared publicly online before it has been checked by peer review.

Example: A news story based on a preprint posted on medRxiv is reporting preliminary results.

See also: Peer Review

Taught in Chapter 20: Be Your Own Scientist: Reading Health Claims.

Preregistration

Publicly recording a study's question, main outcome, and analysis plan before collecting or looking at the results, so readers can check that researchers tested what they said they would.

Example: Clinical trials preregistered on ClinicalTrials.gov get an ID number starting with "NCT."

See also: Primary Outcome, Publication Bias

Taught in Chapter 20: Be Your Own Scientist: Reading Health Claims.

Primary Outcome

The one main measurement a study commits to in advance, before results are known, as the test of whether the treatment works. Other measurements are secondary outcomes.

Example: If a trial's primary outcome shows no benefit but one of ten secondary measures does, the result is much weaker than the headline may suggest.

See also: Preregistration, Statistical Significance

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Prion-Like Spread

The idea that a misfolded protein, such as alpha-synuclein, can pass from one neuron to a connected neuron and make normal copies of the protein misfold, so the damage moves along nerve pathways. It does not mean the disease is contagious between people.

Example: In mice, seeds of misfolded alpha-synuclein injected into the gut wall spread to the brain, but not when the vagus nerve was cut, consistent with prion-like spread.

See also: Alpha-Synuclein, Braak Hypothesis

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Probiotic

Live microorganisms that, when given in adequate amounts, confer a health benefit on the host (ISAPP, 2014).

Example: A capsule of a specific *Lactobacillus* strain that has been shown in trials to help a particular condition fits the definition of a probiotic; a yogurt with no tested benefit does not automatically count.

See also: Prebiotic, Strain Specificity, Probiotic Safety

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Probiotic Safety

The risks of taking live microbes, which are low for most healthy people but higher for people who are very sick, have weakened immune systems, or were born very early, because the microbes can occasionally cause infections.

Example: In October 2023, the FDA warned that probiotics given to preterm infants have caused serious infections, including a death.

See also: Probiotic, Benefit-Risk Balance

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Prodromal Symptoms

Early signs that can appear years before the main symptoms of a disease and before it can be diagnosed.

Example: In Parkinson's, constipation, loss of smell, acting out dreams during sleep, and mood changes can be prodromal symptoms.

See also: Constipation, Gut-First Subtype

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Propionate

The three-carbon short-chain fatty acid. Much of it is taken up by the liver before it can reach the rest of the body.

Example: After a high-fiber meal, propionate made in the colon travels in the blood to the liver.

See also: Short-Chain Fatty Acid, Acetate

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

Psychiatric Comorbidity

The presence of a mental health condition, such as anxiety or depression, in a person who also has another health condition, such as IBD or IBS.

Example: Pooled studies found anxiety symptoms in 32.1% and depression symptoms in 25.2% of adults with IBD, showing how common psychiatric comorbidity is.

See also: Symptom Questionnaire, Integrated Care

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Psychobiotic

In its original 2013 definition by Dinan, Stanton, and Cryan, a live organism that, when taken in adequate amounts, produces a health benefit in patients with psychiatric illness. It is a research term, not an approved product category.

Example: A supplement labeled "psychobiotic" has not been approved by the FDA to treat depression or anxiety.

See also: Probiotic, Replication Failure

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Psychotherapy

Treatment that uses structured conversations and practice with a trained professional, such as a psychologist or licensed counselor, to change patterns of thinking, feeling, behavior, and body responses. It is often called talk therapy.

Example: Cognitive behavioral therapy is one type of psychotherapy.

See also: Brain-Gut Psychotherapy, Cognitive Behavioral Therapy

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Publication Bias

The tendency for studies with exciting, positive results to be published more often and faster than studies that found nothing, so published research makes a treatment look better than it really is.

Example: If five probiotic trials found nothing and stayed unpublished while one positive trial was published, publication bias would mislead readers.

See also: Systematic Review, Preregistration

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Q

Quality of Life

A person's overall sense of well-being across the parts of life that matter to them, including physical health, emotions, relationships, school or work, and daily activities.

Example: In one study of adults with IBD, perceived stigma explained 10% to 22% of differences in health-related quality of life scores.

See also: Illness Burden, Stigma

Taught in Chapter 19: Culture, Food, Family, and Stigma.

R

Randomized Controlled Trial

An experiment in which participants are randomly assigned to a treatment or a comparison condition, so the groups start out alike on average and any difference at the end can be credited to the treatment. It is often shortened to RCT.

Example: The SMILES trial was a small randomized controlled trial of dietary support for depression.

See also: Observational Study, Placebo-Controlled Trial

Taught in Chapter 15: Food and Mood.

Reading an Abstract

The skill of pulling a study's question, methods, main results, and limits out of the short summary at the top of a scientific paper, and comparing what it actually found with how others describe it.

Example: Reading an abstract can reveal that a "probiotic beats depression" headline was based on a mouse study.

See also: Claim-Checking Method, Peer Review

Taught in Chapter 20: Be Your Own Scientist: Reading Health Claims.

Referred Pain

Pain from an internal organ that is felt at a different spot on the body surface, usually skin or muscle supplied by nerves entering the same part of the spinal cord.

Example: In a 1973 study, the same balloon in the lower colon was felt in the lower middle belly by some people and in the sides, rectum, or back by others, showing referred pain.

See also: Visceral Pain, Dorsal Horn

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Regulatory T Cell

A type of T cell that calms or suppresses other immune responses, helping keep the immune system from attacking the body's own tissues or harmless things like food and friendly microbes. It is often shortened to Treg.

Example: Regulatory T cells in the gut help prevent an immune attack on the bacteria in yogurt or the protein in milk.

See also: Adaptive Immunity, Immune-Mediated Disease

Taught in Chapter 4: The Immune System as a Sense Organ.

Remission

A period when IBD is quiet: symptoms fade or disappear, and ideally the inflammation settles too. Remission can last for weeks or years.

Example: The goal of Riya's biologic medicine is to keep her in remission long term.

See also: Disease Flare, Mucosal Healing

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Replication Failure

A situation in which a later study tests the same idea and does not find the original result. It does not automatically mean the first study was wrong.

Example: The strain JB-1 lowered anxiety-like behavior in mice in 2011, but a later trial in 29 healthy men found no such benefit, a replication failure.

See also: Mouse-to-Human Translation, Publication Bias

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Reverse Causation

A situation in which the cause-and-effect arrow points the opposite way from the one assumed.

Example: If depression changes diet and sleep, which then change gut bacteria, a "bacteria cause depression" headline may have reverse causation.

See also: Correlation vs Causation, Confounding Variable

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Rome IV Criteria

The 2016 set of symptom-based diagnostic rules from the Rome Foundation for disorders of gut-brain interaction. For IBS, they require recurrent belly pain on average at least 1 day a week in the last 3 months, linked to two or more of: bowel movements, a change in stool frequency, or a change in stool form, with symptoms starting at least 6 months before diagnosis.

Example: Most published IBS research used the Rome IV criteria, although Rome V, published in May 2026, is now the current version.

See also: Irritable Bowel Syndrome, Positive Diagnosis Strategy

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

S

Sample Size

The number of participants in a study. Small samples give results that swing more by chance and cannot detect uncommon side effects.

Example: A finding in 18 people is a hint, while the same finding in thousands is much more reliable, because sample size matters.

See also: Effect Size, Statistical Significance

Taught in Chapter 13: Autism, ADHD, and the Gut.

Satiety Signal

Any signal from the gut or body that tells the brain enough food has been eaten, producing a feeling of fullness and reducing the urge to keep eating.

Example: Stomach stretch and the release of cholecystokinin during a meal are both satiety signals.

See also: Cholecystokinin, Glucagon-Like Peptide-1 (GLP-1)

Taught in Chapter 2: The Vagus Highway.

School Accommodation

A change in how a student learns, is tested, or participates in school that removes a barrier caused by a health condition or disability, without lowering what the student is expected to learn.

Example: A pass to use the restroom without asking is a common school accommodation for students with IBD.

See also: 504 Plan, Pediatric IBD

Taught in Chapter 19: Culture, Food, Family, and Stigma.

Science Communication

The practice of explaining scientific findings to non-experts accurately, clearly, and with the right level of certainty, without hiding uncertainty or exaggerating results.

Example: Writing "in a study of 67 adults, a diet program helped some people with depression" instead of "diet cures depression" is good science communication.

See also: Claim-Checking Method, Student Research Project

Taught in Chapter 20: Be Your Own Scientist: Reading Health Claims.

Second Brain Metaphor

The comparison of the enteric nervous system to a brain, which highlights that it is large, complex, and able to work independently, but can mislead people into thinking the gut thinks, feels, or decides.

Example: A post saying "your gut has feelings" stretches the second brain metaphor past what the evidence supports.

See also: Enteric Nervous System, Hype Meter

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Selective Eating

Eating a limited range of foods, often because of sensitivity to taste, texture, smell, or appearance, or a strong need for sameness. It is more common in autistic children.

Example: A child who eats only plain pasta and crackers shows selective eating.

See also: Diet as Confounder, GI Symptoms in Autism

Taught in Chapter 13: Autism, ADHD, and the Gut.

Selective Serotonin Reuptake Inhibitor (SSRI)

A type of medicine that blocks the serotonin transporter, so serotonin stays outside cells longer after release. SSRIs such as fluoxetine are prescribed for depression, anxiety disorders, and other conditions.

Example: Because SSRIs also block the transporter in the gut, they can cause side effects such as nausea or loose stools.

See also: Serotonin Transporter, Major Depressive Disorder

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Self-Monitoring

Regularly recording your own symptoms, behaviors, and circumstances, such as sleep, stress, food, activity, and bowel habits, to notice patterns and share accurate information with your care team.

Example: Keeping a two-week diary of sleep, stress, food, and symptoms to bring to an appointment is self-monitoring.

See also: Behavior Change, Talking to Your Doctor

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Self-Stigma

Turning society's negative beliefs about a condition on oneself, such as thinking "I'm disgusting" or "I'm a burden," which can lower self-esteem and confidence.

Example: A teen with IBD who thinks "no one would want to be friends with someone like me" is experiencing self-stigma.

See also: Stigma, Illness Concealment

Taught in Chapter 19: Culture, Food, Family, and Stigma.

Serotonin

A chemical messenger made from the amino acid tryptophan. It acts as a neurotransmitter in the brain, controls movement, secretion, and sensations like nausea in the gut, and is carried in the blood by platelets. It is also called 5-HT.

Example: More than 90% of the body's serotonin is made in the gut, mostly by enterochromaffin cells.

See also: Tryptophan, Enterochromaffin Cell, Gut Serotonin Mood Myth

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Serotonin Transporter

A protein pump in cell membranes that moves serotonin from outside a cell back inside, ending its signal. It is often shortened to SERT.

Example: In the gut, the serotonin transporter on lining cells clears away serotonin after enterochromaffin cells release it.

See also: Selective Serotonin Reuptake Inhibitor (SSRI), Serotonin

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Shared Decision-Making

A process in which a patient (and, for a teen, often their family) and their clinician decide on a treatment together, combining the clinician's knowledge of the evidence with the patient's own values, goals, and preferences.

Example: A doctor laying out the options, including waiting, while the teen and family explain what matters most to them, is shared decision-making.

See also: Benefit-Risk Balance, Talking to Your Doctor

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Short-Chain Fatty Acid

A small fatty acid, with a chain of no more than six carbon atoms, made mainly when gut microbes ferment fiber and resistant starch. It is often shortened to SCFA.

Example: Acetate, propionate, and butyrate are the three main short-chain fatty acids.

See also: Butyrate, Propionate, Acetate

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.

Sickness Behavior

The coordinated set of mood and behavior changes during infection or inflammation, such as tiredness, sleepiness, loss of appetite, low interest, poor concentration, and low mood, driven by immune signals acting on the brain.

Example: Wanting to stay in bed and skip meals when you have the flu is sickness behavior.

See also: Immune-to-Brain Signaling, Inflammatory Depression Theory

Taught in Chapter 4: The Immune System as a Sense Organ.

Sleep and Inflammation

The two-way link between sleep and the immune system: disturbed sleep is associated with higher inflammatory signals in the blood, and inflammation, such as during an infection or flare, can change sleep.

Example: Riya notices she sleeps worse during flares, and poor sleep may in turn feed inflammation, an example of sleep and inflammation.

See also: Teen Sleep Need, Cytokine

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Sleep Architecture

The structure of a night's sleep: the pattern of stages (light non-REM, deep non-REM, and REM sleep) and how they cycle and change across the night.

Example: Deep sleep is more common early in the night and REM sleep later, part of normal sleep architecture.

See also: Circadian Rhythm, Teen Sleep Need

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Sleep Hygiene

The set of everyday habits and bedroom conditions that make good sleep more likely, such as a regular schedule, a dark and cool room, and limiting caffeine and screens before bed.

Example: Charging your phone outside the bedroom is a sleep hygiene habit.

See also: Teen Sleep Need, Behavior Change

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Slow Breathing

Deliberately breathing at a slower-than-usual pace, often around six breaths per minute, with longer, steady exhales.

Example: Breathing in for about four seconds and out for about six is a simple slow breathing exercise.

See also: Heart Rate Variability, Vagal Tone

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Small Bowel Biopsy

The removal of tiny pieces of tissue from the small intestine, usually the duodenum, during an upper endoscopy, so a pathologist can look for villous atrophy and immune cells under a microscope.

Example: After a high tTG antibody result, a small bowel biopsy can confirm celiac disease.

See also: Villous Atrophy, Tissue Transglutaminase Antibody

Taught in Chapter 12: Celiac Disease and Food Reactions.

SMILES Trial

A 12-week randomized controlled trial, published in 2017 by Felice Jacka and colleagues, that tested whether dietitian support toward a Mediterranean-style diet improved symptoms in adults with major depression.

Example: In the SMILES trial, 67 adults took part; 32.3% in the diet-support group reached remission versus 8.0% in the social-support group, but the trial was small, short, and participants knew their group.

See also: Mediterranean Diet, Randomized Controlled Trial

Taught in Chapter 15: Food and Mood.

Smooth Muscle

Muscle made of small, spindle-shaped cells that contract slowly, can stay partly contracted for a long time, and work without conscious control.

Example: You can choose to bend your elbow, but you cannot choose to squeeze your small intestine, because its wall is smooth muscle.

See also: Peristalsis, Interstitial Cells of Cajal

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Somatic Pain

Pain that comes from the skin, muscles, bones, and joints. It is usually sharp or aching and easy to point to.

Example: A paper cut on your finger causes somatic pain you can locate exactly.

See also: Visceral Pain, Referred Pain

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

South Asian Health Context

The cultural, family, migration, and health-system factors that can shape how people with roots in South Asia understand illness, talk about it, and seek care. South Asian communities are enormously diverse.

Example: Understanding the South Asian health context can help a doctor talk with Riya's family about diet and food traditions without stereotyping them.

See also: Migration and IBD Risk, Family Communication

Taught in Chapter 19: Culture, Food, Family, and Stigma.

Spinal Afferent Nerve

A sensory nerve fiber that carries signals from an organ such as the gut to the spinal cord rather than straight to the brainstem, with its cell body in a ganglion beside the spinal cord.

Example: Pain from an inflamed colon travels largely through spinal afferent nerves, so it can still reach the brain if the vagus is cut.

See also: Afferent Signal, Dorsal Root Ganglion

Taught in Chapter 2: The Vagus Highway.

Spore-Forming Bacteria

Bacteria that can survive harsh conditions by forming tough, dormant spores. In the gut, a mix of them dominated by Clostridia has been shown in mice to boost serotonin production by the gut lining.

Example: When germ-free mice received spore-forming bacteria, serotonin in their colon and blood rose toward normal.

See also: Enterochromaffin Cell, Germ-Free Mouse

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Statistical Significance

A label given to a result that would be unlikely to occur by chance alone if there were truly no effect, usually judged by a p-value below a cutoff such as 0.05. It does not show how big or useful an effect is.

Example: In the ATLANTIS trial, amitriptyline's 27-point benefit in IBS scores was statistically significant but smaller than the 35-point difference often considered meaningful to patients.

See also: Effect Size, Sample Size

Taught in Chapter 20: Be Your Own Scientist: Reading Health Claims.

Stigma

A set of negative beliefs and reactions that leads people to label, judge, and treat others as less worthy because of a trait, such as a health condition.

Example: Classmates joking about someone who often leaves for the bathroom is a form of stigma.

See also: Self-Stigma, Mental Health Stigma

Taught in Chapter 19: Culture, Food, Family, and Stigma.

Strain Specificity

The finding that a probiotic's effects belong to a particular strain used for a particular condition, so a result from one strain cannot be assumed to apply to another, even in the same species.

Example: Because of strain specificity, a study showing one *Lactobacillus* strain helps diarrhea says nothing about a different strain sold for mood.

See also: Bacterial Strain, Probiotic

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Stress and Gut Motility

The way stress signals change the speed and pattern of muscle contractions in the digestive tract. In animal studies and small human experiments, stress hormones such as CRH speed up movement in the colon.

Example: Needing to rush to the bathroom before a big performance is an everyday sign of stress and gut motility at work.

See also: Corticotropin-Releasing Hormone, Peristalsis

Taught in Chapter 7: Stress and the Gut.

Stress Response

The set of changes in the brain, nerves, hormones, and immune system that helps the body deal with a challenge, real or perceived, and then return to balance.

Example: A fight with a friend and being out in the cold without a coat can both trigger the stress response.

See also: Fight-or-Flight Response, Hypothalamic-Pituitary-Adrenal (HPA) Axis

Taught in Chapter 7: Stress and the Gut.

Structural vs Functional Disease

The distinction between conditions in which tests show a physical abnormality, such as inflammation, ulcers, a tumor, or a blockage (structural), and conditions in which the organ looks normal on standard tests but does not work normally (functional).

Example: IBD is a structural disease, while IBS has been called a functional disease.

See also: Gut-Brain Interaction Disorder, Irritable Bowel Syndrome

Taught in Chapter 10: IBS and Disorders of Gut-Brain Interaction.

Structure-Function Claim

A statement that a supplement or food supports the normal structure or function of the body without claiming to diagnose, treat, cure, or prevent a disease. Such claims are not preapproved by the FDA.

Example: "Fiber maintains bowel regularity" is a structure-function claim, while "cures IBS" would be a disease claim.

See also: Dietary Supplement Regulation, Health Claim Marketing

Taught in Chapter 20: Be Your Own Scientist: Reading Health Claims.

Student Research Project

A structured investigation in which a student picks one health claim, finds and evaluates the original evidence, assigns a Hype Meter grade, and explains the result in plain language for a real audience.

Example: A science fair poster that grades the claim "kombucha cures anxiety" after reading the original studies is a student research project.

See also: Claim-Checking Method, Science Communication

Taught in Chapter 20: Be Your Own Scientist: Reading Health Claims.

Submucosal Plexus

The inner network of enteric ganglia, lying in the submucosa just under the lining, mainly in the small and large intestines. It mostly controls what the lining does, such as releasing fluid and mucus, and helps sense gut contents. It is also called Meissner's plexus.

Example: The submucosal plexus helps trigger fluid release into the intestine when the lining detects an irritant.

See also: Myenteric Plexus, Gut Wall Layers

Taught in Chapter 1: The Brain in Your Belly (and Why That Phrase Is Misleading).

Sympathetic Nervous System

The branch of the autonomic nervous system that prepares the body for action or stress, often called "fight or flight." It speeds the heart and slows digestion.

Example: When a runner sprints at the end of a race, the sympathetic nervous system holds back gut movement and fluid release.

See also: Parasympathetic Nervous System, Fight-or-Flight Response

Taught in Chapter 2: The Vagus Highway.

Symptom Questionnaire

A standard set of questions, scored with fixed rules, that measures how many symptoms of a condition a person reports and how strong they are. A score above a cutoff "screens positive," but it cannot diagnose.

Example: Many IBD mood studies used a symptom questionnaire, so their numbers describe symptoms, not diagnosed disorders.

See also: Psychiatric Comorbidity, Meta-Analysis

Taught in Chapter 11: Anxiety, Depression, and the Gut.

Synapse

The junction where a neuron passes a signal to another cell, such as another neuron, a muscle cell, or a gland cell, usually across a tiny gap called the synaptic cleft.

Example: An enteric motor neuron passes a "contract" message to smooth muscle at a synapse.

See also: Neurotransmitter

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Synbiotic

A mixture of live microorganisms and substrates selectively utilized by host microorganisms that confers a health benefit on the host (ISAPP, 2020).

Example: A product combining a probiotic strain with a fiber chosen to feed that same strain is a synergistic synbiotic.

See also: Probiotic, Prebiotic

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

Systematic Review

A study of studies that follows a written plan to search for every relevant study on a question, judge each one's quality, and summarize the results, so the conclusion does not depend on which studies an author happened to pick.

Example: A systematic review of probiotics and depression searches several databases with fixed rules rather than citing a few favorite trials.

See also: Meta-Analysis, Publication Bias

Taught in Chapter 16: Probiotics, Prebiotics, and "Psychobiotics".

T

Talking to Your Doctor

The skill of preparing for and taking an active part in medical visits: sharing accurate information, asking questions, and making decisions with your care team.

Example: Writing down your symptoms and three questions before an appointment is part of talking to your doctor.

See also: Shared Decision-Making, Self-Monitoring

Taught in Chapter 19: Culture, Food, Family, and Stigma.

Teen Sleep Need

The amount of sleep recommended for adolescents to support health, learning, and mood: 8 to 10 hours per 24 hours for ages 13 to 18, according to the American Academy of Sleep Medicine.

Example: A teen who sleeps 6 hours on school nights is falling well short of teen sleep need.

See also: Sleep Hygiene, Sleep and Inflammation

Taught in Chapter 18: Sleep, Exercise, and Therapy.

Thalamus

A pair of egg-shaped structures deep in the middle of the brain that relays most incoming sensory information, including pain signals, to the cortex.

Example: A pain signal from the gut passes through the thalamus on its way to the insula.

See also: Insula, Anterior Cingulate Cortex

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Tight Junction

A protein seal that links neighboring epithelial cells near their top edge and controls what can slip through the gaps between them.

Example: Tight junctions let water and some small molecules pass between gut cells but block most larger molecules.

See also: Intestinal Permeability, Zonulin

Taught in Chapter 4: The Immune System as a Sense Organ.

Tissue Transglutaminase Antibody

A blood test that measures antibodies against tissue transglutaminase (tTG), one of the body's own intestinal enzymes; high levels suggest active celiac disease.

Example: A doctor orders a tissue transglutaminase antibody test as a first screen for celiac disease, before the person stops eating gluten.

See also: Celiac Disease, Small Bowel Biopsy

Taught in Chapter 12: Celiac Disease and Food Reactions.

Transmural Inflammation

Inflammation that extends through the entire thickness of the gut wall, from the inner lining to the outer layer.

Example: Crohn's disease causes transmural inflammation, which is why it can lead to fistulas, while ulcerative colitis usually does not.

See also: Crohn's Disease, Gut Wall Layers

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Tricyclic Antidepressant

One of an older class of medicines, named for their three-ring chemical structure, first used for depression and now also prescribed, usually at much lower doses, to reduce chronic pain, including gut pain in disorders of gut-brain interaction. It is often shortened to TCA.

Example: Amitriptyline is a tricyclic antidepressant sometimes used at low doses for IBS pain.

See also: Gut-Brain Neuromodulator, Off-Label Use

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Truncal Vagotomy Studies

Large health-record studies that compare people who had their main vagus nerve trunks surgically cut, usually for ulcers, with people who did not, to test whether cutting the gut-to-brain vagus route lowers later Parkinson's risk.

Example: Truncal vagotomy studies compare full vagotomy with selective vagotomy, which cuts only some branches.

See also: Vagotomy, Braak Hypothesis

Taught in Chapter 14: Parkinson's, Alzheimer's, and the Gut.

Tryptophan

An essential amino acid, meaning the body cannot make it and must get it from protein in food. It is the raw material for serotonin and can cross the blood-brain barrier.

Example: Eggs, milk, seeds, and meat all supply tryptophan.

See also: Serotonin, Kynurenine Pathway

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Tryptophan Hydroxylase

The enzyme that performs the first and key step in making serotonin from tryptophan. It comes in two versions: TPH1, mainly in gut enterochromaffin cells, and TPH2, mainly in neurons.

Example: Because the brain uses its own tryptophan hydroxylase (TPH2), it makes its own serotonin separately from the gut.

See also: Serotonin, Enterochromaffin Cell

Taught in Chapter 5: Chemical Messengers and the Serotonin Myth.

Tumor Necrosis Factor

A pro-inflammatory cytokine, made by immune cells such as macrophages, that drives and sustains inflammation in tissues. It is often written TNF or TNF-alpha.

Example: Anti-TNF medicines block tumor necrosis factor to calm inflammation in Crohn's disease.

See also: Cytokine, Anti-TNF Therapy

Taught in Chapter 4: The Immune System as a Sense Organ.

U

Ulcerative Colitis

A form of inflammatory bowel disease in which inflammation affects only the colon and rectum, starting at the rectum and spreading upward in one continuous stretch, and stays in the inner layers of the gut wall. It is often shortened to UC.

Example: A person whose colonoscopy shows continuous inflammation from the rectum partway up the colon may have ulcerative colitis.

See also: Inflammatory Bowel Disease, Crohn's Disease

Taught in Chapter 9: Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's.

Ultra-Processed Food

A food made by industrial formulation, mostly from substances extracted or derived from foods, often with additives such as flavors, colors, or emulsifiers not used in home kitchens. The term comes from the NOVA classification system.

Example: Many packaged snacks and sugary soft drinks count as ultra-processed food.

See also: Dietary Pattern, Observational Study

Taught in Chapter 15: Food and Mood.

Unneeded Restrictive Diet

Cutting out foods or whole food groups without a diagnosed medical reason, which can bring costs such as nutrient gaps, missed or delayed diagnoses, extra expense, and social stress, without a proven benefit.

Example: Going gluten-free "just in case" before a celiac test is an unneeded restrictive diet that can also make the test unreliable.

See also: Gluten-Free Diet, Eating Disorder Risk

Taught in Chapter 12: Celiac Disease and Food Reactions.

V

Vagal Tone

The ongoing, background level of activity in the vagus nerve's motor fibers, most often estimated through its calming effect on the heart.

Example: Even at rest, vagal tone gently brakes your heart, keeping it slower than it would otherwise beat.

See also: Heart Rate Variability, Vagus Nerve

Taught in Chapter 2: The Vagus Highway.

Vagotomy

Surgery that cuts all or part of the vagus nerve to the stomach, historically done to reduce stomach acid in people with ulcers.

Example: Surgeons performed many vagotomies for peptic ulcers starting in the 1940s.

See also: Vagus Nerve, Truncal Vagotomy Studies

Taught in Chapter 2: The Vagus Highway.

Vagus Nerve

A long, mixed nerve (cranial nerve X) that runs from the medulla through the neck and chest into the abdomen, carrying sensory and motor fibers to and from organs such as the heart, lungs, and digestive tract.

Example: Most vagus nerve fibers carry signals from the body to the brain; classic fiber counts in animals put the figure at about 80%.

See also: Afferent Signal, Efferent Signal, Nodose Ganglion

Taught in Chapter 2: The Vagus Highway.

Vagus Nerve Stimulation

A treatment that delivers mild electrical pulses to the vagus nerve, through a device implanted under the skin or a handheld device placed on the skin, to change nerve signaling to the brain or body. It is often shortened to VNS.

Example: Vagus nerve stimulation is FDA approved for some kinds of epilepsy and depression but is not approved for Crohn's disease, IBS, or anxiety.

See also: Implanted VNS Device, Noninvasive VNS, Vagus Nerve

Taught in Chapter 17: Medicine for the Gut-Brain Axis.

Villous Atrophy

The shortening and flattening of the intestinal villi, seen under a microscope, that is the hallmark damage of celiac disease.

Example: A biopsy showing villous atrophy in the duodenum supports a diagnosis of celiac disease.

See also: Intestinal Villi, Small Bowel Biopsy

Taught in Chapter 12: Celiac Disease and Food Reactions.

Visceral Hypersensitivity

A lowered threshold for feeling sensations from internal organs, so that normal amounts of gut stretch or activity are felt as uncomfortable or painful.

Example: In balloon tests, many people with IBS report pain at lower balloon volumes than other people, a sign of visceral hypersensitivity.

See also: Balloon Distension Test, Central Sensitization, Irritable Bowel Syndrome

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Visceral Pain

Pain that comes from internal organs such as the stomach, intestines, bladder, or heart. It tends to feel dull, crampy, or deep, and is hard to pinpoint.

Example: The vague, crampy ache of gas trapped in the intestines is visceral pain.

See also: Somatic Pain, Visceral Hypersensitivity

Taught in Chapter 8: Pain, Sensitivity, and the Gut.

Z

Zonulin

A protein that some researchers propose loosens tight junctions in the small intestine. It has been reported to be the same molecule as a blood protein called pre-haptoglobin 2, and its role is still debated.

Example: Widely used commercial zonulin tests detect other blood proteins, so a "high zonulin" result does not show that a gut is leaky.

See also: Tight Junction, Leaky Gut Claim

Taught in Chapter 6: Fiber, Fatty Acids, and the Blood-Brain Barrier.