# Food and the Gut–Brain Axis

Understanding food signaling and epigenetics



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# Introduction

A meal is one of the most ordinary events in a day.

You make toast, warm a bowl of soup, or eat something left over from the night before. You notice the taste, perhaps the company, perhaps how little time you have before the next thing begins.

Food is broken down. Nutrients are absorbed. Cells detect what has arrived and adjust their activity. Microbes use some of the materials your own digestive enzymes leave behind. Nerves and hormones help coordinate the response.

Yet you know something about the connection between digestion and experience. You may have felt your appetite disappear before a difficult conversation, noticed your stomach tighten with worry, or found that digestive discomfort changes how you approach the day.

These familiar experiences offer an entrance into a much larger story: the continuing exchange of information among food, the gut, its microbial inhabitants, and the brain. This book asks how a meal becomes part of the chemical environment in which cells live, and how that environment can influence the way cells use their genes.

You do not need a background in microbiology or genetics to follow the story. We will introduce each idea as it becomes useful, beginning with events you can picture: eating breakfast, feeling hungry, responding to stress, and choosing what to cook.

One idea will guide the journey: signaling. A signal is something a cell detects that changes its activity. A chemical encounter can lead a cell to release another molecule, change its metabolism, or alter which genes it uses.

Food contributes to these interactions while supplying energy and materials for growth and repair. The digestive system breaks food into components the body can absorb, and nerves and hormones coordinate much of that work. Cells in the stomach and intestine release hormones that help regulate digestion; nervous pathways carry information within the digestive tract and between the gut and brain.[1]

The brain can influence the movement and secretions of the gut. Information from the gut helps the brain regulate eating and other bodily functions. Immune activity and molecules carried through the bloodstream add further routes of communication.

Together, these interacting pathways form what researchers call the *gut–brain axis*. The intestine is home to communities of bacteria and other microorganisms. As they obtain energy and materials, they transform substances around them. Some of their products become available to our cells, connecting microbial activity with the body’s own chemistry.

Genes contain instructions that cells use to carry out their work. Most cells in your body contain essentially the same DNA, yet an intestinal cell and a nerve cell have very different jobs. They use different portions of those instructions.

DNA is packaged with proteins, including proteins called histones. The organization of that packaging, along with chemical modifications to DNA and its associated proteins, helps regulate access to genetic information. Epigenetics concerns this layer of regulation without changing the underlying DNA sequence.[2]

Some regulatory states persist as cells divide; others change with current conditions. We will distinguish a temporary response from evidence of lasting biological memory. Food enters this story through several routes. Nutrients supply materials used in cellular chemistry. Microbial products can interact with receptors or enzymes. Hormonal and immune signals can influence the proteins that regulate gene activity.

Experiments with cells allow researchers to examine individual mechanisms closely. Animal studies make it possible to investigate interactions across tissues and development. Human studies show what happens in people, although they differ greatly in what they can establish.

A study observing that two things occur together asks a different question from a trial that deliberately changes an exposure. A change in an inflammatory marker is a different outcome from an improvement in symptoms. A result in mice can reveal a mechanism that still needs testing in humans.

We will follow the meal into the digestive tract and explore how the gut detects what has arrived. We will trace communication toward the brain and back again, then enter the microbial world where food becomes new molecules.

From there, we will look inside cells to understand how DNA is packaged and how gene activity is regulated. That foundation will help us examine where nutrients and microbial products meet epigenetic mechanisms.

The later chapters bring these processes together. Stress and inflammation reveal how signals can reinforce or restrain one another. Development and biological memory show how timing can shape a response and sometimes leave lasting effects. Finally, we return to the table to consider practical choices that fit the evidence and ordinary life.

Food carries culture, pleasure, habit, convenience, and care. What we eat depends on what is available, affordable, familiar, and comfortable to digest. Health also reflects circumstances that no individual meal can control.

The story begins with something you have done thousands of times. You sit down to eat. Let’s follow what happens next.

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2. National Human Genome Research Institute. Epigenomics Fact Sheet. Accessed November 21, 2026.

# Chapter 1: A Meal Becomes a Message

The oatmeal is still warm when you add the berries. A spoonful of plain yogurt settles into the middle of the bowl. You stir, take a bite, and glance at the clock.

There is nothing unusual about this breakfast. It might be something you eat most mornings, without giving it much thought. You notice the tartness of the yogurt, the sweetness of a berry, the texture of the oats. Perhaps you are already thinking about the day ahead.

Inside your body, however, breakfast is becoming a series of events that you will never consciously feel. Muscles move. Enzymes work. Cells detect the arrival of nutrients and release chemical messengers. Nerves carry information. Later, microbes will use portions of the meal that your own digestive enzymes cannot break down. Some of the substances they produce will interact with the machinery that regulates gene activity.

Two connected areas of biology will help us follow the meal: signaling, through which cells respond to information, and epigenetic regulation, which involves DNA and its packaging. We will begin with the signals and return to the underlying machinery in Chapters 4 and 5.

Our journey begins before the first spoonful reaches your stomach. The sight and smell of food help prepare the digestive system for what is coming. Your mouth produces saliva. As you chew, you break the meal into smaller pieces, and enzymes begin working on its starch. After you swallow, coordinated muscular contractions move the food down your esophagus.

The stomach receives and mixes it. Acid and enzymes help dismantle proteins. Gradually, the stomach releases its contents into the small intestine, where digestive enzymes and bile help make nutrients available for absorption.

Throughout this process, nerves and hormones coordinate what happens next: when to release digestive juices, how to move the contents along, and how to respond to the arrival of food. Digestion requires communication from the beginning.[1]

A cell has no understanding of breakfast. It responds to physical and chemical changes. A molecule encounters a receptor—a protein capable of recognizing and responding to it—and that encounter can set off a sequence of events inside the cell.

Think of pressing a doorbell. The pressure of your finger becomes an electrical signal, which produces a sound somewhere else. The person inside does not need to see your finger to know that something has happened at the door.

Biological signaling works through transformations like these. A chemical encounter at a cell’s surface may change its electrical activity, release another molecule, or alter the activity of proteins inside it. The response depends on the receiving cell and the machinery it contains.

Scattered among the cells lining the intestine are specialized cells that detect nutrients. Some release hormones. Some also communicate directly with nerves. In a study published in 2018, researchers working with mice investigated intestinal sensory cells called *neuropod cells*. These

cells formed connections with neurons belonging to the vagus nerve, a major communication route between internal organs and the brain.

At these connections, the gut cells released glutamate, a chemical messenger. Glutamate crossed the tiny gap between cells and activated the receiving neuron. Experiments showed that communication across this connection could happen within milliseconds.

This was a striking demonstration of how a nutrient-related event inside the intestine could be translated into a rapid neural signal. The researchers had identified a physical connection and tested how it worked.[2]

One gut hormone is called glucagon-like peptide-1, usually shortened to GLP-1. It participates in the regulation of blood glucose and appetite. Its role in appetite has been tested directly in people. In a controlled study, researchers gave twenty healthy men either an infusion of GLP-1 or a saline comparison infusion. With GLP-1, the participants reported greater fullness after breakfast and ate less at a later lunch.

An infusion is a carefully controlled experiment, with a defined exposure. It does not tell us exactly what our bowl of oatmeal will do. It does show that changing a particular chemical signal can change an aspect of eating behavior in humans.[3]

The bowl is empty. You rinse it, put it aside, and get on with your morning. The meal continues through your digestive tract. To follow the next part of its story, we need to slow down and travel farther.

Some of the carbohydrates in the oats and berries resist digestion by your own enzymes. Portions reach the large intestine, where microbes have access to them. These organisms possess biochemical tools that expand what can be done with food. Through fermentation, they transform certain carbohydrates into smaller compounds, including the short-chain fatty acids acetate, propionate, and butyrate.

Their destination matters. A substance produced inside the colon does not automatically reach every organ in the same amount. In a study of twelve healthy adults, scientists delivered labeled short-chain fatty acids to the colon and followed their fate. The proportion reaching the wider circulation differed substantially among the three compounds; much of the butyrate was used before it could circulate throughout the body.[4]

Certain gut cells have receptors that respond to short-chain fatty acids. In experiments using mice and cells taken from mouse intestines, researchers found that these molecules could stimulate GLP-1 release. Removing particular receptors reduced that response.

The experiments connected a microbial product to a receptor and then to a hormone. They revealed one possible route by which microbial activity can influence the body’s signaling systems. How strongly that route operates after a particular human meal requires its own investigation.[5]

Already, our breakfast has become difficult to describe as a single event. Different ingredients take different paths. Some responses begin quickly; others depend on food reaching microbes

farther along the intestine. A molecule can be transformed, absorbed, consumed by a cell, or used to trigger another response.

Some of these pathways reach the regulation of genes. Before following them in detail, it helps to picture the material they encounter. Most of your cells contain essentially the same DNA, yet an intestinal cell and a nerve cell perform very different jobs. Each uses a particular selection of the information available to it.

DNA is wrapped around proteins called histones. Together, DNA and its associated proteins form *chromatin*. How this material is organized helps determine which parts of the DNA are accessible to the machinery that reads genes.

Cells can also attach chemical marks to DNA and histones. These marks help regulate gene activity without changing the underlying sequence of DNA letters. DNA methylation and histone modifications are two major components of epigenetic regulation.

Imagine a large reference library. Possessing every book does not mean consulting every page at once. The organization of the collection influences what can be found and used. In a cell, that organization is physical, chemical, and continually regulated.[6]

Scientists can make the connection between food and DNA packaging tangible by following the carbon. In experiments reported in 2022, researchers gave mice dietary fiber containing a traceable form of carbon. That label allowed them to track material from the fiber through subsequent chemical transformations.

They detected fiber-derived carbon in small chemical attachments called acetyl groups on histones in intestinal lining cells. Microbial metabolism had helped connect dietary material to a modification of the host’s DNA-packaging proteins.

The result made an otherwise abstract relationship tangible. Material that began in dietary fiber could become part of the chemistry associated with gene regulation. It established that connection in mouse intestinal tissue. It did not establish that a bowl of oatmeal changes a person’s brain epigenetically, improves their mood, or creates a lasting biological memory. Those are additional questions, each requiring additional evidence.[7]

Where does that leave the brain? We have encountered a neural route from the gut, a hormone capable of influencing appetite, and microbial products that can interact with receptors and gene-regulating processes. These are different kinds of evidence, gathered in different experiments.

Connecting them into a complete explanation of a human experience—feeling satisfied after breakfast, craving a snack, responding to stress—requires more work. A plausible chain of events becomes convincing when researchers can test its links, including the points where signals change form or pass between tissues.

By lunchtime, breakfast may have slipped from your attention. Its components have entered processes that continue without your awareness.

The bowl sits on the drying rack. Inside the body, the meal’s story is still unfolding. To understand how it becomes part of experience, we first need to follow the communication between gut and brain.

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# Chapter 2: How the Gut Talks—and the Brain Answers

The next morning, you make the same breakfast.

Oatmeal, berries, a spoonful of yogurt. The bowl is warm in your hands. You sit down and take the first few bites. Then your phone lights up.

A meeting has been moved forward. There is something you need to prepare, and less time than you expected. You read the message twice. Perhaps your appetite fades. Perhaps you notice a tightening in your abdomen or an urge to get up and move.

The first chapter followed food into the body. This morning asks us to follow information in both directions: the gut is responding to the meal while the brain responds to the world around you.

Figure 1 maps the main routes we will follow. The arrowheads show how influence travels in both directions.

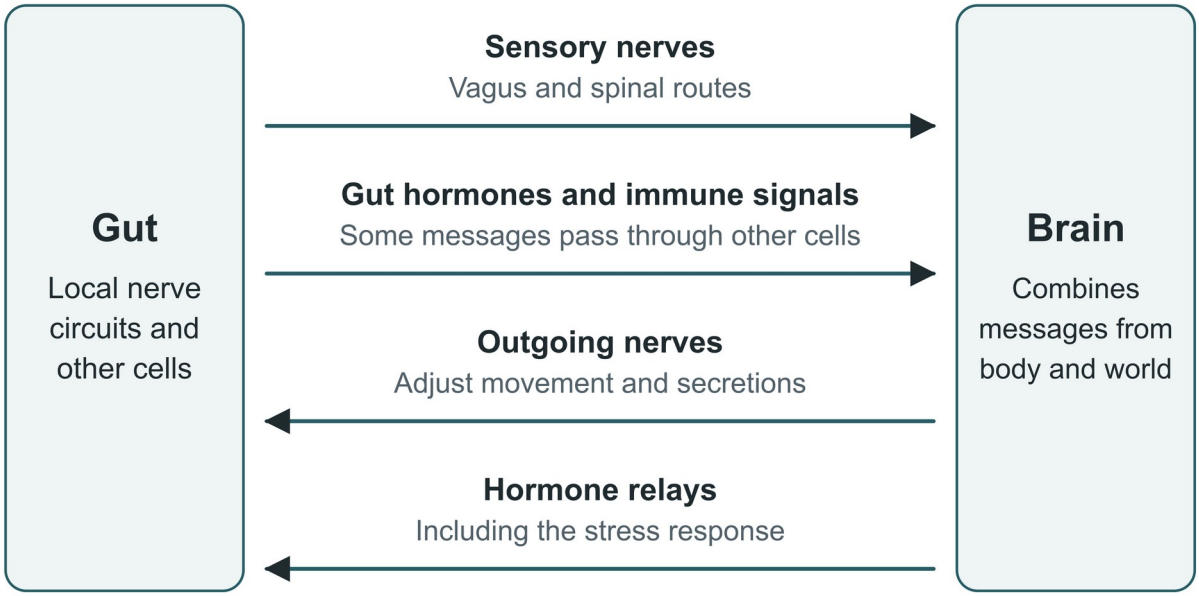



**Figure 1. How the gut and brain exchange messages.** Arrows show the direction of influence, including relays through nerves, hormones, and other cells. A gut molecule need not enter the brain to affect its activity. The routes interact, and the gut also has local nerve circuits.

Sources: this chapter, references 1, 2, and 8; Chapter 6, reference 7.

To understand the exchange, we first need to look at the nervous system already present inside the gut. Within the walls of the digestive tract lies a network called the *enteric nervous system*. Its neurons help coordinate muscular contractions, relaxation, and the release of digestive secretions.

Much of this work happens without your attention. You do not have to decide when a section of intestine should contract. Local circuits respond to conditions in the gut and organize the next movement.

This network is connected to the brain and spinal cord, allowing local activity to be adjusted as the body's needs change. Digestion combines regulation within the gut with communication beyond it.[1]

Some of the information generated in the gut travels toward the brain through the vagus nerve. Despite its singular name, the vagus contains many nerve fibers with different functions. Sensory fibers carry information toward the brain. Motor fibers carry signals outward toward organs.

A nerve signal is a traveling change in electrical activity along a cell's membrane. At many connections between cells, the signal is passed onward through the release of a chemical messenger. Information can therefore change form as it moves through the system: a physical stretch becomes electrical activity, which leads to chemical release, which changes the activity of another cell.

Experiments recording vagal sensory neurons in mice have shown that different groups respond to different events, including stomach stretch and nutrients in the intestine. The vagus carries several kinds of information about what is happening inside the body.[2]

Consider stretch. As food enters and moves through the digestive tract, it changes the shape and tension of the tissues surrounding it. Specialized sensory endings respond to these mechanical changes. They give the nervous system information about the physical presence of a meal.

In a study published in 2019, researchers identified distinct groups of vagal sensory neurons in mice and tested what happened when they activated them. Stimulating certain neurons associated with intestinal stretch reduced feeding and changed activity in brain circuits involved in hunger.

This helped establish that a mechanical event in the intestine could influence eating through a specific neural route. The gut was providing information that the brain could use to adjust behavior.[3]

Other sensory routes reach the central nervous system through the spinal cord. These pathways contribute to the detection of events in the gut, including potentially painful ones. Research mapping sensory neurons from the mouse colon has revealed several distinct populations, each with its own pattern of molecular equipment.

The anatomical picture is therefore a network of specialized pathways. Different parts of the gut, and different kinds of disturbance, can recruit different messengers.[4] Much of the incoming information helps regulate the body without becoming a conscious sensation. You feel the overall experience of fullness, hunger, comfort, or discomfort. You do not normally feel each nerve signal contributing to it.

And the brain receives information from outside the body at the same time. The sight of breakfast matters. So do its smell and availability. Researchers demonstrated this particularly clearly by recording the activity of hunger-related neurons in awake mice. When food appeared, some of those neurons changed their activity before the animals had eaten anything. The response depended partly on the animals' nutritional state and the food presented.

The brain could begin adjusting its activity in anticipation of eating. Signals arriving later from the digestive tract would provide additional information about what had actually been consumed.[5]

For our breakfast story, this gives us a useful way to think about the brain's role. It combines incoming information rather than waiting for one final report from the stomach.

Hormones add another layer. Alongside GLP-1, another gut hormone involved in the response to food is cholecystokinin, shortened to CCK. In a small human study, researchers delivered fat directly into the upper small intestine and measured participants' responses. CCK levels rose, and participants reported greater fullness. When researchers administered a drug that blocked a particular CCK receptor, that increase in fullness was reduced.

The experiment tested the receiving end of the message. It provided evidence that CCK signaling contributed to the sensation being measured. The study's reduction in actual food intake did not reach conventional statistical significance, a reminder that fullness ratings and the amount someone eats are related but distinct outcomes.[6]

A hormone can influence a response without determining it completely. Eating takes place within a system receiving many inputs. Measuring one messenger gives us part of that system.

Hormonal and neural routes also intersect. A chemical released by a gut cell can act on a nearby nerve, which then carries information onward. The message may begin as a molecule and continue as electrical activity.

Now turn the direction around. The brain can influence digestive activity through outgoing nerves that act on circuits in the gut. These signals help adjust muscular movement and secretion. They operate alongside the local enteric network, allowing digestion to respond to circumstances beyond the intestine itself.

The same meal can therefore enter a digestive system whose activity is being shaped by other demands on the body. If the message on your phone is experienced as stressful, neural and hormonal responses can alter digestive activity. Researchers have measured such changes in people.

In one study, twelve healthy volunteers underwent two different challenges: a demanding listening task and intermittent immersion of a hand in cold water. Sensors recorded pressure changes inside the colon.

Both challenges increased colonic motor activity compared with their control conditions, but the patterns differed. The psychological challenge produced a response that remained elevated during the recovery period.

The study showed that the type of challenge mattered. "Stress" described more than one physiological pattern.[7] One of the hormonal pathways involved in responding to stress is the *hypothalamic–pituitary–adrenal axis*, usually called the HPA axis.

The hypothalamus, a region of the brain, releases a signal that acts on the pituitary gland beneath it. The pituitary releases a hormone called ACTH into the circulation. ACTH reaches the adrenal glands, above the kidneys, and stimulates the production of cortisol.

Cortisol helps coordinate aspects of metabolism and the response to stress. It also participates in feedback: rising cortisol can reduce the signals that stimulate further production. A signal leaves the brain, changes hormone production elsewhere, and returns information that helps regulate the system.[8]

This is an example of a feedback loop. The outcome of a process influences the activity that produced it. The immune system participates in this exchange too.

Immune cells release chemical messengers called cytokines, which help coordinate responses across tissues. Information about inflammation can also reach the brain, sometimes through a relay involving cells at the boundary between blood and brain. We will examine these routes more closely in Chapter 6.

Microbial metabolism adds further chemical inputs. As the short-chain fatty acid experiments in Chapter 1 showed, a microbial product can act on a gut cell that releases a hormone; the initial molecule and the eventual message need not be the same substance.

There is another question beneath all these routes: what determines how a cell responds when a signal arrives? The response also depends on the receiving cell's receptors, active proteins, and organization of genetic material. Chapters 4 and 5 will examine that machinery. First, we need to understand the organisms supplying some of the chemical inputs.

Back at the table, you put down your phone. The meeting is still approaching. You decide what needs to be done first and take another spoonful of oatmeal. Perhaps your appetite returns; perhaps you set the bowl aside for later.

Within the body, information has been moving along several routes. Some has concerned the food itself. Some has concerned the situation in which you are eating. The gut and brain have been participating throughout, with local nerves, hormones, and other cells helping coordinate the exchange.

Later, portions of the breakfast will reach organisms that possess their own ways of processing it. Those microbes will change the chemical materials available to the cells around them.

To follow the meal farther, we now need to enter their kitchen.

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# Chapter 3: The Microbial Kitchen

By the time you begin thinking about lunch, breakfast has become something quite different from the meal you remember.

The berries have lost their shape. The yogurt has mixed with digestive fluids. Much of the meal's digestible carbohydrate, protein, and fat has been broken down and absorbed. Other material continues along the intestine.

Among it are carbohydrates that your digestive enzymes could not fully dismantle. When these reach the large intestine, they enter a place where different biochemical tools are available. Microbes carry enzymes capable of performing reactions that our own cells cannot. They can open up some of the food structures we leave behind and use the resulting material for their metabolism and growth.

Figure 2 separates the microbial transformation of food from the response inside a receiving cell.

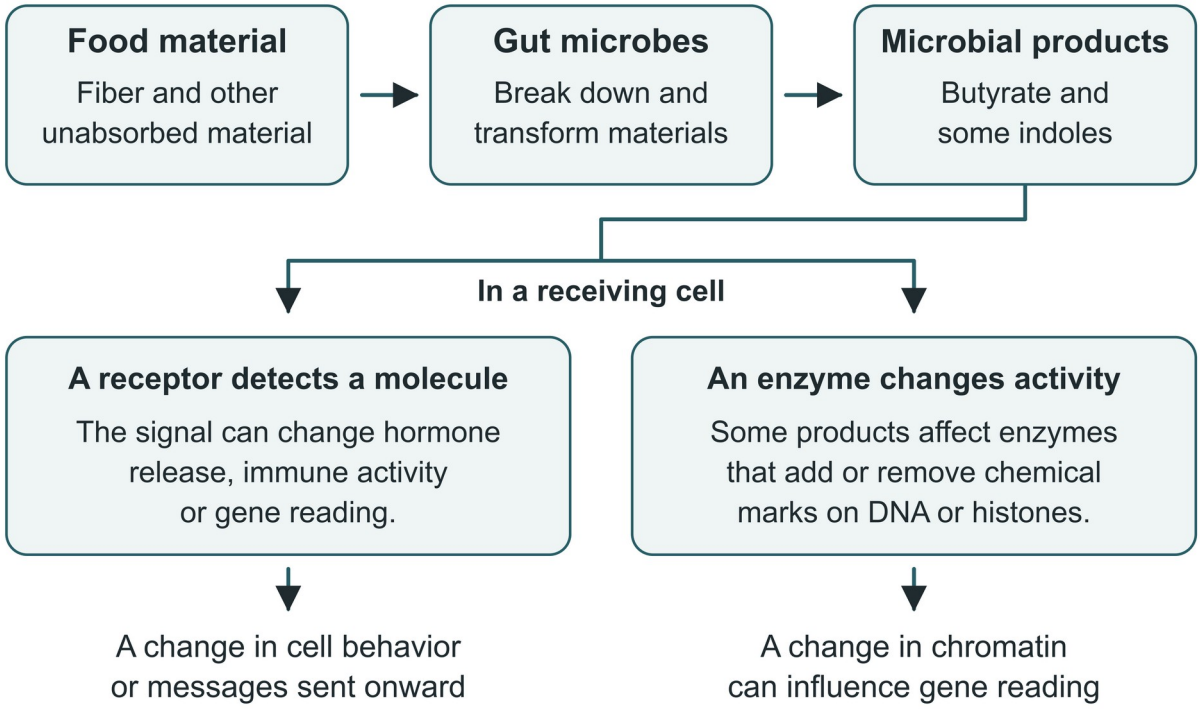



**Figure 2. From food material to a cellular response.** The two routes can interact. For example, some indoles activate a receptor that helps regulate transcription, while butyrate can affect enzymes that remove acetyl groups from histones. These mechanisms depend on the molecule and cell; receptor signaling alone does not establish a lasting epigenetic change.

Sources: this chapter, references 2 and 5; Chapter 1, reference 5; Chapter 5, reference 8.

To follow this part of breakfast's journey, imagine entering a kitchen that has been operating continuously since long before your meal arrived. There is no single cook. Different organisms

have different equipment. Ingredients pass between them, and the product of one reaction can become the starting material for another.

The kitchen's output depends on what arrives, which organisms are present, and what they are doing. Its products are metabolites: substances produced or used during metabolism. The name identifies their place in biochemical reactions, rather than a particular function or health effect.

Even the word *fiber* conceals considerable variety. Dietary fibers differ in their chemical structure and in how easily microbes can reach and break their bonds. An organism equipped to use one carbohydrate may be poorly equipped to use another.

Researchers demonstrated this with a species called *Ruminococcus bromii*. In laboratory experiments using resistant starch—a form of starch that escapes digestion in the small intestine—this bacterium was particularly effective at initiating its breakdown. Its activity also made material available to other organisms.

The finding helped explain why a microbe can have an influence larger than its own contribution to the final products. It may make an ingredient accessible to the rest of the community.[1]

Scientists call the exchange of materials between microbes *cross-feeding*. In kitchen terms, one organism prepares an ingredient that another can use. In chemical terms, enzymes break bonds, molecules are transformed, and products move between cells.

This makes the community important. Knowing that a particular organism can produce a molecule in a laboratory does not tell us how much it will produce inside a person. It must have the necessary starting materials and suitable conditions. Other organisms may supply what it needs, compete for the same resources, or consume what it makes.

One familiar result of microbial carbohydrate fermentation is the production of acetate, propionate, and butyrate. As the human tracing study in Chapter 1 showed, production in the colon does not determine how much reaches the wider circulation.

Production is the beginning of a molecule's story. It may be consumed by another microbe, absorbed by an intestinal cell, changed by the liver, or carried onward. Its biological effect depends on which of those events occurs.

Butyrate illustrates how a microbial product can connect metabolism with immune regulation. In mouse experiments, it promoted the development of regulatory T cells, which help restrain immune responses. Researchers also observed increased histone acetylation around a gene important to these cells' identity. The study linked a microbial metabolite, a modification associated with gene regulation, and an immune-cell response.[2]

The microbial kitchen also helps explain why people can respond differently to the same food. In a human study of resistant-starch supplementation, researchers measured changes in the microbiota and in short-chain fatty acids found in stool. Butyrate concentrations rose across the study population overall, but individual responses varied considerably. Some participants showed substantial increases; others remained low.

The investigators explored how those differences related to the organisms present in each person's microbial community.[3] The measurement itself deserves attention. Stool contains what

remains after production, microbial use, absorption, and intestinal transit. Its butyrate concentration is not a direct measure of everything that was produced or everything the body received.

Two people may eat similar breakfasts while delivering the ingredients to communities with different capabilities. Even within one person, the activity of those communities can change. Carbohydrates are only part of the supply arriving in this kitchen.

Proteins contribute another set of ingredients: amino acids. Most dietary protein is digested and absorbed before reaching the colon, but some protein-derived material remains available to microbes. Material originating from the body itself also contributes to the intestinal supply.

One amino acid of particular interest is *tryptophan*. Our own cells use tryptophan in several pathways. Microbes possess additional ways to transform it, producing a family of compounds that includes indole and related molecules.

Small differences among those molecules can alter which cells respond to them and how. Researchers have investigated this chemistry by changing the bacteria themselves. In one study, scientists worked with a gut bacterium capable of producing indole-3-propionic acid, often abbreviated IPA. They disrupted a gene required for a metabolic pathway and compared the altered bacterium with its usual form in mice.

The change affected the compounds found in the animals. In an experiment using a defined community of microbes, IPA was detectable in mice carrying the usual bacterial strain but undetectable in those carrying the altered strain.

Changing a bacterial gene had changed part of the host's circulating chemistry.[4] The bacterial gene supplied instructions for microbial metabolism. The resulting molecule could then encounter the host's cells. Those host cells had their own receptors, enzymes, and gene-regulating machinery.

Another tryptophan-derived molecule, indole-3-aldehyde, provides an example of what can happen at the receiving end. In mouse experiments, researchers linked its production by certain lactobacilli to the activation of a receptor called the *aryl hydrocarbon receptor*, or AHR. This receptor can influence gene transcription—the process through which information in DNA is copied into RNA.

The pathway contributed to production of an immune messenger called interleukin-22, or IL-22, and to protective responses at mucosal surfaces. The sequence connected microbial metabolism to a receptor, then to gene activity and an immune response.[5]

AHR provides a route to gene regulation through a receptor that also functions as a regulator of transcription. Activating it can change gene activity without, by itself, establishing a persistent epigenetic change. Chapter 5 will distinguish this route from the effects of metabolites on enzymes that modify chromatin.

Both mechanisms belong in our story. Keeping them distinct helps us understand exactly what a microbial molecule is doing. The tryptophan story also reaches the nervous system.

In experiments involving mice with an induced autoimmune inflammatory disease of the central nervous system, researchers investigated cells called *astrocytes*. These cells help maintain the environment in which neurons function and participate in responses to injury and inflammation.

The researchers found that microbial products of tryptophan metabolism could influence inflammatory activity through AHR signaling in astrocytes. Manipulating the diet, microbial activity, and receptor pathway helped identify connections among them.

This provided evidence for a mechanism linking microbial metabolism to responses in cells of the central nervous system. The experiments concerned a particular disease model; they did not establish that increasing dietary tryptophan improves mood or brain health in people.[6]

Bile acids bring a different kind of ingredient into the microbial kitchen. Their story begins in the liver, which makes primary bile acids from cholesterol. Released into the intestine as part of bile, they help the body handle dietary fats. Much of the bile-acid supply is subsequently reabsorbed and recycled.

Microbes modify some of the molecules they encounter along this route. Their enzymes can remove attached groups or change other features of the chemical structure, generating secondary bile acids and further derivatives.

Scientists have reconstructed one major bacterial conversion pathway using purified enzymes. By combining the necessary enzymes and starting materials, they could reproduce the transformation outside the bacterium.

That work identified the biochemical machinery behind a process taking place within the gut.[7] The modified molecules can, in turn, affect the host's cells. One bile-acid-sensing receptor is called TGR5. Experiments in cells and mice have linked activation of this receptor to the release of GLP-1, the hormone we encountered in the previous chapters. Researchers used both receptor-directed compounds and genetic approaches to test its role.

A molecule associated with digestion could therefore participate in a signaling pathway that influences hormone release.[8] Other bile-acid derivatives can interact with machinery involved in deciding what an immune cell becomes.

In experiments reported in 2019, researchers screened bile-acid metabolites and identified two derivatives with different effects on T cells. One bound directly to a transcription factor involved in the development of a particular inflammatory T-cell population. Another promoted the development of regulatory T cells under the conditions studied.

The compounds were chemically related, yet their effects differed. A relatively small structural change could alter how a molecule interacted with the host's biology.[9] The same care applies to the microbes producing it. Their names tell us who may be present. To understand what is happening, we also need to know which pathways are active and which products are being made.

Human dietary experiments show that this activity can respond to changing food supplies. In a short controlled study, participants ate diets composed entirely of animal or plant products. Researchers observed changes in microbial community composition and gene expression, along with differences reflecting carbohydrate and protein metabolism.

The study demonstrated that the human gut microbiome could respond rapidly to a substantial dietary change. It also showed why studying microbial activity adds information beyond counting organisms.[10]

The breakfast's components have entered overlapping processes. Some material has been used directly by your cells; some has become available to microbes. The body has supplied additional ingredients and absorbed some of the results.

The kitchen metaphor helps us picture the transformations, but the kitchen has no chef planning a menu for our benefit. Each organism uses the opportunities available to it. Our cells encounter the resulting chemistry.

A molecule may activate a receptor on a cell's surface. It may enter a cell and influence an enzyme. It may contribute material to a chemical mark on a histone. Each route gives us a different way to investigate how food can become biologically consequential.

For the gut–brain axis, the next task is to follow those consequences: whether they remain local, change an immune or hormonal message, or reach cells within the nervous system.

For epigenetics, we must look more closely at the receiving cell.

Inside the nucleus, DNA is packaged, made accessible, read, and regulated. The next chapter follows the microbial products to the machinery of the receiving cell.

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# Chapter 4: How Cells Read Their Genes

Imagine following one of the molecules from the microbial kitchen into a cell lining your intestine.

At this scale, breakfast has disappeared. There are no oats, berries, or spoonfuls of yogurt. There are molecules moving through a crowded environment, encountering other molecules, entering reactions, and being transformed.

Within the cell lies a compartment called the nucleus. Inside it is most of the cell's DNA. The intestinal cell contains instructions for making far more kinds of proteins than it needs at any particular moment. A nerve cell elsewhere in your body carries essentially the same genetic information, yet it performs a very different job.

The difference depends partly on which instructions each cell uses, when it uses them, and how much of their products it makes. To understand how food and signaling might influence that reading, we first need to understand what the process involves—and how the instructions are stored.

Figure 3 previews the role of packaging. Chromatin is DNA together with its associated proteins; its arrangement helps shape access to the instructions.

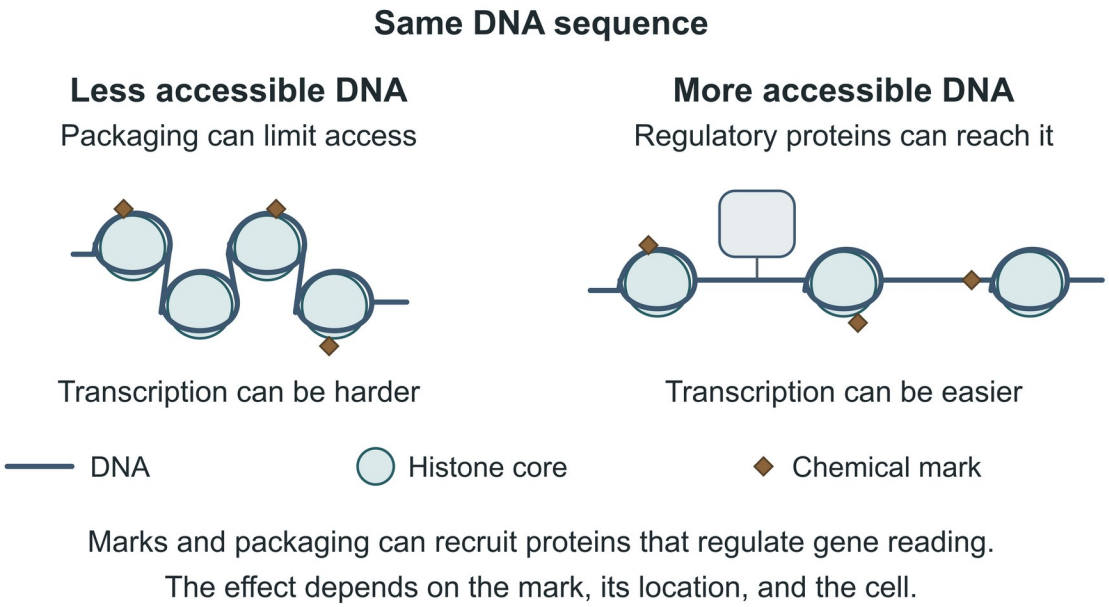



**Figure 3. DNA packaging influences how genes are read.** DNA winds around histone cores. The small rounded shape touching exposed DNA represents a regulatory protein. Marks occur in both arrangements; their meaning depends on their type and location. These are simplified possibilities, not fixed on–off states. The drawing is not to scale, and greater access does not guarantee transcription.

Sources: this chapter, references 3, 5, 6, 7, and 10.

DNA is a long molecule whose sequence contains biological information. Scientists represent its four chemical bases with the letters A, C, G, and T. Their order matters.

A gene is a region of DNA containing information used to produce a functional RNA or, through an RNA intermediate, a protein. For a protein-coding gene, the first major step is *transcription*. An enzyme called RNA polymerase helps produce an RNA copy of the information. After processing, the resulting messenger RNA can leave the nucleus and be used by ribosomes, the cellular machinery that assembles proteins.

That second process is called *translation*. The RNA sequence guides the assembly of amino acids into a protein. Some other RNAs perform their functions without becoming templates for proteins.[1]

When scientists say a gene is more active, they may mean that more RNA is being produced from it. That can influence how much protein is made, although additional controls operate between the RNA and the finished protein.

The familiar phrase “turning a gene on” is therefore a useful beginning. Actual gene regulation also involves changes in amount, timing, and duration. Proteins called *transcription factors* help regulate this process. They recognize particular DNA sequences and work with other proteins to increase or decrease transcription. Signals arriving from outside the cell can alter their activity.

In this way, a chemical event at the cell’s surface can eventually influence which genetic instructions are used inside the nucleus.[2] DNA is not stretched out in the nucleus as a freely accessible line of letters. Much of it is wrapped around groups of proteins called histones. A segment of DNA wound around a histone core forms a unit called a *nucleosome*.

You can picture thread wrapped around a small spool. Along a stretch of DNA, many such units are connected. Researchers have determined nucleosome structures in extraordinary detail. A landmark study published in 1997 showed how DNA winds around a core of eight histone proteins and makes numerous contacts with them.

The arrangement is a physical structure, with surfaces and binding sites that other molecules must encounter.[3] DNA together with its associated proteins is called *chromatin*. The way chromatin is arranged influences access to the underlying DNA. If a regulatory sequence is occupied or difficult to reach, a protein that recognizes that sequence may have less opportunity to bind.

Chromatin organization also changes. Cells contain molecular machines that use energy to rearrange nucleosomes, changing how DNA is exposed. These are called *chromatin-remodeling complexes*. Structural studies of a human remodeling complex have shown how its components engage a nucleosome. Experiments altering those components have helped reveal which contacts are necessary for remodeling activity.

The packaging is being managed by machinery capable of doing physical work.[4] Enzymes can attach small chemical groups to DNA or histone proteins. Other proteins can recognize some of those modifications, and other enzymes can remove or alter them.

Epigenetic regulation involves changes to DNA and its associated proteins that influence gene activity without changing the underlying DNA sequence. Some mechanisms help maintain cellular identity; others participate in responses to current conditions.[5]

We have already encountered one kind of histone modification: acetylation. An acetyl group is a small chemical group that enzymes can attach to particular sites on histones. The attachment changes the chemistry of that site. It can affect interactions within chromatin and create a feature that another protein recognizes.

In a carefully controlled experiment, researchers produced histones carrying an acetyl group at one specific position. They then assembled those histones with DNA and examined the resulting structures.

That modification reduced the formation of compact arrangements under the experimental conditions. A small chemical change had altered the behavior of the larger structure.[6] Researchers studying a protein region called a *bromodomain* showed that it could specifically recognize acetylated sites. This helped explain how a chemical modification could recruit additional machinery.

The mark had become something another molecule could detect.[7] The proteins involved are often described as writers, readers, and erasers. Writers install a modification, readers recognize it, and erasers remove it. A reader protein has a structure that allows it to interact with a particular modified site; its effect depends on the machinery linked to it.

Methylation shows why location matters. Methyl groups can be attached to DNA or to histones, producing distinct modifications on different molecules. Even among histone modifications, the position matters.

Methylation at one site on a histone can be associated with active genes and help recruit machinery involved in chromatin remodeling. Methylation at another site can participate in maintaining a repressed region.

Experiments have identified proteins that recognize these different marks and connect them to different molecular activities.[8,9] DNA methylation gives us another way to see the importance of readers.

In mammals, a common form involves adding a methyl group to the DNA base cytosine, often where a cytosine is followed by a guanine. Scientists call these locations CpG sites.

Methylation in certain gene-control regions can contribute to reduced transcription. One mechanism involves proteins that recognize methylated DNA and bring other regulatory machinery to it. In experiments studying the protein MeCP2, researchers found a connection between recognition of methylated DNA and a protein complex containing histone deacetylases —the enzymes that remove acetyl groups.

A modification on DNA could therefore become connected to changes in histone-associated regulation.[10] DNA methylation, histone modifications, transcription factors, and remodeling proteins can influence one another. A cell’s regulatory state emerges from their combined activity.

This also means that seeing a mark beside an active or inactive gene does not, on its own, establish what caused the gene's behavior. The mark might help produce the state. It might help maintain it. It might appear as a consequence of transcription or accompany another process responsible for the change.

To test cause and effect, researchers can deliver an enzyme to a chosen location in the genome. In a study published in 2015, researchers adapted a CRISPR-based targeting system so that it could position an acetylating enzyme at selected sites without cutting the DNA. The enzyme added acetyl groups to nearby histones, and targeted genes became more active.

The researchers tested sites near the beginnings of genes, called *promoters*, as well as regulatory regions called *enhancers*. Targeting the enzyme to either kind of region could increase transcription in the settings examined.

This provided evidence that directing acetylation machinery to particular locations could help cause gene activation.[11] There is then a second question: how long does the effect last?

A cell may increase transcription while a signal is present and return toward its previous state after the signal fades. Other responses can persist longer. DNA methylation provides a concrete example. Before a cell divides, it copies its DNA. Each new double-stranded DNA molecule contains an older strand and a newly made strand.

At a previously methylated site, the older strand can retain its mark while the new strand initially lacks the corresponding modification. Proteins can recognize this partially marked arrangement and help the methylation machinery restore the pattern.

Structural research on one such recognition protein, UHRF1, showed how it interacts with methylated DNA. This work helped explain a molecular step in maintaining methylation after DNA replication.[12]

Histone-associated systems have their own maintenance mechanisms. In the repressive histone system mentioned earlier, recognition of an existing mark can stimulate machinery that installs additional marks. Such feedback can help reinforce a chromatin state.

In 2021, a team reported a tool called CRISPRoff. It directed machinery that established DNA methylation and repressive histone modifications at selected genes in cultured cells. A temporary exposure to the tool could initiate gene repression that continued through subsequent cell divisions. In some experiments, repression also persisted as stem cells developed into neurons. Companion approaches could reactivate silenced genes.

These experiments showed that a transient intervention could establish a maintained regulatory state without changing the targeted DNA sequence.[13] Here, cellular memory means retention of a regulatory state after the initiating intervention has gone. Chapter 7 will distinguish this persistence within a cell lineage from inheritance between generations.

The cell's genetic information has a physical setting. DNA is wrapped around histones and associated with regulatory proteins. Access can change, marks can be installed or removed, and some patterns can be maintained. Different tissues provide different combinations of these features.

The intestinal cell continues absorbing, metabolizing, maintaining its boundaries, and responding to neighboring cells. Inside its nucleus, genetic information is being used selectively. Some products are needed for its ordinary work. Others may be needed as circumstances change.

We can now ask more precisely how nutrients and microbial products interact with this machinery under conditions that exist in the body. The next chapter follows those encounters, where food meets gene regulation.

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# Chapter 5: Where Food Meets Gene Regulation

A methyl group is a small thing: one carbon atom joined to three hydrogen atoms.

In the previous chapter, we saw how attaching such a group to DNA or a histone can influence the interactions that regulate gene activity. We also met acetyl groups, which participate in another set of modifications to DNA-packaging proteins.

The enzymes that install methyl and acetyl groups need a supply of material and suitable conditions in which to work. Enzymes that remove or alter marks depend on the chemistry around them too. This brings us back to food.

The machinery inside the nucleus participates in the cell's metabolism—the network of reactions through which the cell obtains energy, builds molecules, and maintains itself. Some of the materials passing through that network began in a meal. Others have been recycled from molecules already present in the body.

To understand food's influence on gene regulation, we need to follow the transformations between what we eat and what an enzyme encounters inside a cell. Digestion releases amino acids, which the body can use to build new proteins or direct into other metabolic pathways. One of these amino acids, methionine, contributes to the production of a molecule called *S-adenosylmethionine*, usually shortened to SAM.

SAM carries methyl groups that enzymes can transfer to other molecules, including DNA and histones. Its supply is connected to a wider network called *one-carbon metabolism*. The name refers to reactions that transfer small units containing a single carbon atom. Folate participates in these transfers and helps support the recycling of methionine. Vitamin B12 is involved in that recycling pathway as well.

These familiar nutrients are part of the chemistry that supplies methylation reactions.[1] Choline contributes to this network too. The body can convert some choline into betaine, which participates in a route that helps regenerate methionine.

Choline also has other jobs, including supporting cell membranes and the production of the neurotransmitter acetylcholine. A nutrient can therefore enter several pathways, with its use depending on the needs and capabilities of the receiving tissues.[2]

When an enzyme transfers SAM's methyl group to another molecule, SAM becomes *S-adenosylhomocysteine*, or SAH. This product matters because it can inhibit methylating enzymes. The chemistry depends on both the available donor and what happens to the products of the reaction.

Researchers tested this connection by changing methionine availability in cultured cells. They observed changes in SAM and SAH, changes in particular histone methylation marks, and changes in gene transcription. Restoring methionine could restore the affected methylation state.

Related experiments in mice linked dietary methionine changes to metabolism and histone methylation in the liver.[3] In an analysis of eighty-seven older adults participating in a randomized trial, researchers examined blood-cell DNA before and after two years of folic acid and vitamin B12 supplementation or placebo. The participants had been selected for mildly elevated homocysteine, a compound involved in methionine metabolism.

The researchers identified differences in methylation changes at several DNA regions between the groups. Evidence at individual measured sites was more limited. The findings showed that a nutritional intervention could be associated with specific changes in adult blood-cell DNA methylation. They did not establish that those changes improved brain function or represented a general improvement in the epigenome.[4]

Researchers studying choline intake during the third trimester of pregnancy compared two controlled intake levels and examined the placenta and umbilical-cord blood. For two genes involved in cortisol regulation, the higher-choline group showed greater promoter methylation in placental tissue but lower promoter methylation in cord-blood white cells. The researchers also observed lower placental expression of the gene encoding corticotropin-releasing hormone, part of the hormonal system we met in Chapter 2.

The same dietary comparison produced different methylation patterns in different tissues. The study did not establish lasting effects on the children's stress responses or mental health.[5]

The enzymes that attach acetyl groups to histones commonly obtain those groups from *acetyl-CoA*. This molecule occupies an important position in metabolism, connecting several pathways involved in energy use and the construction of other molecules.

Researchers demonstrated one connection between glucose metabolism and histone acetylation by studying an enzyme called ATP-citrate lyase. The enzyme helps convert citrate into acetyl-CoA. In mammalian cell experiments, its activity was needed for particular increases in histone acetylation associated with growth signals and differentiation. Glucose availability influenced histone acetylation through this pathway.

The study connected nutrient processing to the supply of material used by chromatin-modifying enzymes.[6] The cell's metabolism and its gene-regulating machinery therefore influence one another. Changes in nutrient processing can affect chromatin, while changes in gene activity can alter the enzymes used to process nutrients.

Vitamin C provides an example of a nutrient that supports the activity of an enzyme. TET enzymes chemically modify methylated cytosine in DNA. These reactions can participate in pathways leading to the loss of DNA methylation; they begin transformations that other processes carry forward.

In experiments with cultured mouse embryonic stem cells, adding vitamin C increased TET activity and changed DNA modifications. This was followed by reduced methylation at many gene promoters and changes in the expression of particular genes.

When researchers removed two relevant TET enzymes, the vitamin-C-induced changes in DNA modifications were lost. That helped establish the enzymes' role in the response.[7] It does not tell

us that additional vitamin C will reproduce the same response in a well-nourished adult. The cells' starting conditions, developmental state, and nutrient exposure were part of the experiment.

Butyrate brings microbial metabolism into this chemistry. It can serve as fuel, and its metabolism can contribute to acetyl-CoA, which supplies groups for histone acetylation. Under appropriate conditions, butyrate also inhibits histone deacetylases, enzymes that remove acetyl groups. Experiments comparing cellular metabolic states show that the balance between these actions depends on the exposure and how the cell processes it.[8]

How much butyrate reaches a cell, and how rapidly the cell uses it, can determine its effect. The arrangement of the tissue influences both. The lining of the colon contains small pocket-like structures called *crypts*. Stem and progenitor cells near their bases help replenish the lining. More mature cells occupy positions closer to the intestinal contents.

In experiments involving mice and intestinal cells, researchers found that mature colonocytes consumed butyrate. Their metabolism helped limit the amount reaching the proliferating cells deeper in the crypt.

When stem and progenitor cells were more directly exposed, butyrate could suppress their proliferation. The experiments linked this response to a transcription factor called FOXO3. The tissue's architecture and the metabolism of neighboring cells helped determine which cells encountered the microbial product.[9]

Even within a tiny region of the intestine, cells can experience different chemical conditions. A substance abundant near the gut contents may be consumed before it reaches a nearby population.

In the body, digestion, microbial metabolism, absorption, and tissue organization all help determine the exposure. Researchers have also examined the microbiota's relationship with chromatin across several tissues.

In a mouse study, investigators compared animals raised without microbes with animals carrying a microbiota. They measured histone modifications in tissues including the colon, liver, and fat.

The differences depended on diet. Many microbiota-associated chromatin changes observed with a diet rich in complex carbohydrates were absent under the study's high-fat, high-sugar dietary conditions. Giving short-chain fatty acids to germ-free mice reproduced aspects of the histone-modification patterns and gene-expression responses associated with microbial colonization.[10]

The study also left useful questions open. A metabolite supplied to an animal can act through several routes. Reproducing a chromatin pattern does not prove that the molecule acted directly on the histones or enzymes in every tissue examined.

Receptor-mediated signaling provides another route. The tryptophan-derived compounds and AHR pathway described in Chapter 3 show how a microbial molecule can influence transcription through a receiving protein. This differs from supplying an acetyl group or directly inhibiting an enzyme that modifies chromatin.[11]

A nutrient may supply a chemical group. A vitamin may support an enzyme's activity. A microbial product may inhibit an enzyme or activate a receptor. The eventual response depends on the machinery present in the cell.

Timing also enters the mechanism. In mouse experiments, researchers found that the microbiota influenced daily rhythms in the activity of histone deacetylase 3, or HDAC3, in intestinal lining cells.

Microbes affected the enzyme's expression, and its recruitment to chromatin varied rhythmically. These patterns were connected to changes in histone acetylation, metabolic gene activity, and nutrient uptake.

The study showed that microbial influence could extend to the timing and organization of gene regulation.[12] The brain introduces an additional set of questions. A food-related change in intestinal gene activity might alter a hormone or immune signal that subsequently influences the brain. In that case, the relevant epigenetic event could occur in the gut.

A different claim would be that a dietary or microbial molecule reaches the brain and changes chromatin within a neuron or another brain cell. To follow the first route, researchers need to identify the altered intestinal response and the message it sends onward. To follow the second, they need evidence about exposure within the brain and the response of the relevant cells.

Blood measurements can help establish what is circulating. They cannot, by themselves, tell us what is happening to chromatin inside a particular brain region. A change in a nutrient level, a histone mark, an RNA molecule, and a person's experience are different observations. Connecting them requires evidence that the intermediate steps occurred and contributed to the outcome.

Food's nutrients enter a body with existing stores, active enzymes, and established patterns of gene regulation. Its fermentable components reach microbes with their own capabilities. The resulting molecules encounter tissues that absorb, consume, transform, and respond to them.

Those circumstances include the signals arriving from other systems. An immune response changes the chemical environment. Stress recruits neural and hormonal pathways. Changes in the gut can send information back toward the brain.

The next chapter brings these processes together, following the feedback loops among stress, inflammation, and the gut.

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# Chapter 6: Stress, Inflammation, and Feedback Loops

The meeting from Chapter 2 is over, but imagine that your abdomen has not settled. You have answered the immediate question and returned to your work. The discomfort keeps drawing your attention.

Now the sensation itself becomes a concern. You begin wondering whether it will return during the next meeting. Information from the gut is contributing to the circumstances that sustain the stress response.

This is a feedback loop: the consequences of a process return to influence it. Some loops restrain a response, while others reinforce it. Understanding the difference helps explain how stress and inflammation can interact, and how responses can settle.

The stress response has useful work to do. As we saw in Chapter 2, autonomic signals can change digestive activity, and different parts of the gut need not respond in the same way. Human experiments have measured changes in colon activity during stressful tasks.[1]

The HPA pathway adds a hormonal relay: signals from the hypothalamus stimulate the pituitary, which releases ACTH and prompts the adrenal glands to produce cortisol. Cortisol helps coordinate energy use and regulates immune activity. It also feeds information back to the brain and pituitary, helping reduce further stimulation of its own production. This is one of the body's negative feedback systems.[2]

"Negative" describes the direction of the effect: the response pushes back against the change that helped produce it. A thermostat provides a familiar comparison. As a room warms toward the chosen temperature, the heating system receives a signal to reduce its output.

Inflammation is a coordinated response to threats or tissue damage. Immune cells detect trouble, release signals, recruit other cells, and help organize defense and repair. Among their signals are cytokines: small proteins that change the behavior of cells carrying the appropriate receptors. Some encourage immune activity. Others help contain it. Their effects depend on where they are released, which cells receive them, and what other signals are present.

In the intestine, this coordination is particularly demanding. Food and microbes are always nearby. The immune system must respond effectively to danger while tolerating much of what normally passes through or lives within the gut.

Inflammation can also remain concentrated in a particular tissue. A local immune response in the intestinal lining and a rise in inflammatory markers throughout the bloodstream are different observations. Neither can be inferred simply from the sensation of an unsettled stomach.

Stress, digestive symptoms, and inflammation can overlap. They are not interchangeable measurements. The gut's nervous system includes neurons and supporting cells called enteric glia. Glia help maintain the environment in which neurons operate, and they also communicate with surrounding tissues.

In a study published in 2023, researchers exposed mice to repeated stress and examined experimental colitis, an inflammatory condition of the colon. Glucocorticoids—the hormone family that includes human cortisol—acted on enteric glia, shifting some of them into a state that encouraged inflammatory immune activity. The evidence supported a relay involving glial signals, recruitment of immune cells called monocytes, and production of the inflammatory messenger TNF. Disrupting parts of this pathway reduced the worsening of colitis associated with stress.[3]

This provides a concrete route from a stress hormone to cells in the gut and onward to immune activity. It does not establish that an anxious morning causes inflammatory bowel disease. The mice had experimentally induced disease, and the detailed mechanism still requires further testing in people.

There is an apparent puzzle here. Cortisol can restrain inflammation. How can stress hormones also participate in processes that make inflammation worse? The answer depends partly on the receiving cell and the duration of exposure. A hormone does not carry one instruction that every tissue follows identically.

In human studies involving controlled exposure to cold viruses, researchers examined stressful life experiences and the responsiveness of immune cells to glucocorticoids. Prolonged threatening experiences were associated with reduced sensitivity to these hormones. Reduced sensitivity, in turn, predicted greater illness risk or stronger inflammatory responses after viral exposure. The amount of circulating cortisol alone did not explain the findings.[4]

These were respiratory infection studies, and people were not randomly assigned to stressful lives. They support a model rather than proving every step. Their broader lesson is nevertheless valuable: measuring a messenger does not tell us everything about whether its message is being heard.

The intestinal lining must allow absorption while managing contact with the contents of the digestive tract. Its epithelial cells, the junctions between them, and the overlying mucus all contribute to that task.

Permeability describes how readily particular substances cross a barrier. It is a measurable property, and the result depends on what is being measured, where, and under which conditions.

In one small human study, public speaking increased a measure of intestinal permeability, particularly among participants who showed a cortisol response. Another stressful challenge in the same research did not produce the same effect. Additional experiments involving a stress hormone and a drug that stabilizes mast cells supported a role for these immune cells in the response.[5]

Later work illustrates why the details matter. In a study published in 2025, administering corticotropin-releasing hormone, or CRH, to healthy volunteers did not change permeability in the sampled upper small intestine under the testing conditions. Applying CRH directly to tissue outside the body produced a different result.[6]

A change in the passage of a small test molecule also does not establish that bacteria are entering the bloodstream. Keeping those distinctions clear allows us to discuss the barrier without turning every digestive symptom into evidence of a damaged intestine.

The return journey, from immune activity toward the brain, can involve sensory nerves or cells at the boundaries between blood and brain. These cells can receive an immune message and produce another signal, relaying information without every original messenger entering brain tissue.

Fever offers a clear example. In experiments in mice, researchers showed that production of a messenger called prostaglandin E2 by cells lining the brain's blood vessels was crucial for generating fever after an inflammatory challenge. Those vessel cells helped translate information about inflammation into a change in temperature regulation.[7]

Immune activity can also influence emotional experience. In a randomized experiment involving 115 healthy adults, participants received either saline or a small dose of endotoxin, a bacterial component that stimulates immune responses. Those receiving endotoxin developed higher levels of inflammatory cytokines and, on average, reported greater depressed mood and feelings of social disconnection over the following hours.[8]

The experiment used a carefully controlled injection. It was not a test of ordinary digestion, and the temporary mood changes were not equivalent to a diagnosis of depression. What it demonstrated was a direction of influence: an experimentally stimulated immune response could alter subjective experience.

In the meeting example, abdominal discomfort draws your attention, concern about symptoms sustains stress, and stress may further influence gut function. This illustrates one possible reinforcing loop; it does not establish that every part of the immune pathways just described is involved.

In reinforcing, or positive, feedback, "positive" means that a change encourages more change in the same direction. Such a loop can involve sensations, attention, and nervous system activity without requiring substantial inflammation. In other circumstances, immune signaling may contribute. There is no single loop that explains every person's symptoms.

Nor does participation of the brain make symptoms voluntary. Sensation, attention, hormonal release, and intestinal movement are physical processes. Understanding their interaction gives us more places to investigate; it gives us no basis for blaming someone for being ill.

Microbes participate in these exchanges while also responding to the environment that the body creates. In earlier chapters, we followed microbial products toward host cells. Inflammation can send influence in the opposite direction by changing the conditions in which microbes live.

In experiments in mice, researchers found that intestinal inflammation generated nitrate that certain bacteria could use in energy production. This gave *Escherichia coli* a growth advantage in the inflamed intestine. Bacteria lacking the machinery needed to use nitrate lost that advantage.[9]

This matters when interpreting a microbiome sample. Finding a different microbial community in an inflamed gut does not, by itself, reveal which change came first. Microbes may influence inflammation, inflammation may reshape the microbial community, and both processes may operate together.

A cell receiving a stress hormone or an immune messenger may alter which genes it transcribes. That changes the proteins it can make, including receptors, enzymes, and additional signaling molecules. The response can therefore alter how the cell participates in the next round of communication.

Cortisol provides a direct connection to the mechanisms discussed in the previous chapters. It binds a glucocorticoid receptor that can influence gene activity. Where that receptor acts depends partly on chromatin—the DNA and associated proteins—and which regions are accessible.

Experiments comparing cell types have shown that much of glucocorticoid receptor binding occurs at regions of chromatin that were already accessible before hormone exposure. The same hormonal signal encounters different arrangements of accessible DNA in different cells.[10]

This is one point where stress signaling and epigenetic regulation meet. Chromatin helps shape the response to a signal, while signaling can also influence chromatin and the machinery that regulates genes.

Whether a change in gene activity persists after the stimulus ends is a further question. We will examine that question in the next chapter. First, the loops have another essential feature: ways to end.

Restraint and recovery are built into the system. Ending an inflammatory response involves active work. Macrophages, immune cells that engulf material in tissues, help clear cells that have reached the end of their lives. In experiments with human cells, macrophages that engulfed dying neutrophils changed their signaling behavior, reducing production of several inflammatory messengers and increasing signals involved in restraint. Cleanup helped change the instructions being sent through the tissue.[11]

By late afternoon, the discomfort may have settled without your noticing the exact moment. That familiar recovery deserves a place in the story alongside the processes that sustain a response.

The harder questions arise when demands repeat, an inflammatory trigger persists, or one part of the system changes the conditions faced by the others. Then the timing of a signal becomes as important as its identity. A brief exposure, repeated pulses, and a sustained signal can produce different outcomes.

The next question is how that state changes over time: which responses fade, which leave a trace, and when an experience becomes part of the conditions under which the body receives its next message.

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# Chapter 7: Timing, Development, and Biological Memory

Across the breakfast table, a young child is learning to use a spoon. You help with a mouthful, then return to your own meal.

You share a setting, but your bodies bring different histories to it. Daily rhythms, recent meals, and earlier exposures shape the conditions in which each receives food.

In the child, the immune system, microbial community, and nervous system are still undergoing changes that make some experiences particularly influential. The same nutrient can encounter tissues at a different developmental stage.

A molecule's effect depends on more than its identity and concentration. It also depends on when it arrives, how long it remains, how often it returns, and what has happened before.

Recall the doorbell from Chapter 1. A single ring, repeated rings, and a button held down are different patterns. Cells also respond to patterns through receptors, enzymes, and gene regulation.

Cortisol, the hormone we followed in the previous chapter, provides an example. Its release has a daily rhythm, with shorter pulses superimposed on that rhythm. In experiments using cultured cells and animal models, researchers found that pulses of glucocorticoid hormones produced corresponding cycles of receptor activity and gene transcription. Continuous exposure produced a different pattern of gene activity. The pauses were part of the biological information.[1]

When hormone concentrations fell, receptors could disengage from particular DNA regions. When another pulse arrived, the system could respond again. A single blood measurement would capture only one moment in that changing process. It might tell us how much hormone was present at that instant while missing the pattern surrounding it.

Circadian rhythms are biological rhythms that run on an approximately twenty-four-hour cycle. The body contains interacting clocks, including a central clock in the brain and molecular clocks in other tissues. Their coordination helps organize when different activities occur.

In a small laboratory study, ten healthy young men followed an early meal schedule and then a schedule shifted five hours later. The later meals shifted the daily rhythm of blood glucose and the timing of activity of a clock gene in fat tissue. The measured rhythms of melatonin and cortisol did not shift in the same way.[2]

The study did not identify a universally ideal breakfast hour. It showed that meal timing could change the relationship between some of the body's rhythms. Duration matters within these rhythms as well. A brief signal may activate proteins already present. A longer exposure may allow changes in transcription and the production of additional proteins. Those proteins can alter the next response, sometimes reinforcing it and sometimes limiting it.

A developing tissue contains cells that are acquiring different identities and arranging themselves into a working structure. Signals help coordinate that process. The duration of exposure can contribute to the instructions.

In experiments with developing chick neural tissue, researchers studied a signaling protein with the memorable name Sonic hedgehog. Both its concentration and the duration of its signaling influenced which developmental genes became active. Cells also gradually reduced their responsiveness through a feedback mechanism. They were integrating the strength of the signal with how long it acted.[3]

Once a cell has taken on a particular identity and become part of a tissue, the consequences can outlast the signal that helped guide it. A temporary instruction can contribute to a lasting structure.

This helps explain the idea of a sensitive period: a stage during which a particular experience has an especially strong influence on a developing system. Sensitive periods differ among tissues and functions. There is no single moment when the whole body finishes being shaped by experience.

In the gut, the transition from milk toward solid foods brings changes in the materials available to microbes and the signals encountered by the immune system. Researchers studying mice found a distinctive immune response around weaning. Interfering with this response increased susceptibility to certain inflammatory conditions later in life. Protection was associated with the development of regulatory T cells, immune cells that help restrain other immune responses. Microbial short-chain fatty acids and retinoic acid, a molecule made from vitamin A, contributed to this process.[4]

The mouse study does not provide a feeding calendar for human infants. It demonstrates, under experimental conditions, that the same developing system can have different needs and responses at different stages.

The gut’s relationship with the stress system also has a developmental dimension. In a foundational mouse study, animals raised without microbes showed an exaggerated hormonal response to restraint stress. Introducing a conventional microbial community earlier in development partly corrected that response; introducing it at a later stage did not produce the same correction.[5]

This supported the existence of a developmental window in that experimental model. Germ-free mice are an unusual biological condition, however. Their results cannot tell us that an individual child’s future stress responses have been fixed by an early microbial event.

Human evidence presents a different challenge. We cannot assign people to severe deprivation to test its lifelong effects. Sometimes historical events create circumstances that researchers can study decades later.

During the Dutch Hunger Winter of 1944–1945, severe food shortages affected part of the Netherlands. Researchers later compared people exposed around conception with their unexposed, same-sex siblings. About six decades afterward, those exposed had, on average,

lower DNA methylation at a region associated with IGF2, a gene involved in growth. Exposure later in pregnancy was not associated with the same difference at that region.[6]

These measurements came from adult blood. They did not show the methylation pattern at birth or establish that the difference caused a particular disease. Famine also brings many intertwined hardships. The results support a connection between early conditions and later epigenetic differences, while leaving important questions about the intervening mechanism.

Biological memory means that a previous experience changes a later response or state. It does not require awareness or the machinery used to remember a face or a conversation.

Memory can reside in tissue organization, the abundance or behavior of cells, or patterns of gene regulation. Chapter 4 showed how methylation and other regulatory systems can help maintain a state. Immune experiments let us test the consequences of an earlier encounter.

Researchers can expose cells to a stimulus, remove it, allow time to pass, and then challenge the cells again. If the later response differs from that of previously unexposed cells, they can investigate what carried the effect across the interval.

In experiments with human monocytes, a type of immune cell, brief exposure to a fungal cell-wall component helped produce a stronger response to a later challenge. This phenomenon is called trained immunity. It was associated with changes in histone methylation, linking altered responsiveness to the regulation of DNA packaging.[7]

Further work compared different initial stimuli as monocytes developed into macrophages. Some exposures produced heightened later responses; others produced reduced responsiveness, called tolerance. The resulting cells showed different patterns of gene activity and histone marks.[8]

A stronger immune response may help in one setting and contribute to harm in another. A reduced response may prevent excessive inflammation or leave the body less able to respond effectively. The consequences depend on the challenge and the tissue.

These experiments used isolated cells and defined stimuli. They establish mechanisms that can support cellular memory. Whether an ordinary dietary exposure produces a comparable lasting effect requires its own evidence.

Some immune cells are relatively short-lived, raising another question: how can a change in responsiveness outlast the original cells? One possibility involves the cells that produce their replacements.

In a human study of BCG vaccination, researchers examined blood and bone marrow before and after vaccination. Three months later, they found changes in gene activity in bone marrow stem and progenitor cells—the cells from which new blood cells develop—alongside epigenetic and functional changes in circulating monocytes.[9]

The vaccination study also illustrates why “the cell remembers” can be too simple. Sometimes the relevant unit is a continuing system of cell production, differentiation, and communication. In the previous chapter, we followed feedback loops in which one response helped sustain another. Such a loop can continue even if no single cell carries a permanent epigenetic change. Repeated exposure can also maintain a state by continually renewing the signal.

These possibilities matter when interpreting research. An effect observed for several weeks might reflect a lasting cellular change, a signal that remains present, or an exposure that keeps recurring.

Recovery also matters. In the human dietary experiment introduced in Chapter 3, an animal-based diet altered microbial community structure within days. The measured community structure returned toward its original state shortly after the diet ended. A rapid response did not establish a permanent change.[10]

For food and the gut–brain axis, this is an essential distinction. A meal can generate a real biological response without leaving a lasting imprint. Repeated meals may sustain conditions that a single exposure does not. Some developmental effects may persist even after the original conditions have changed.

A methylation pattern maintained as one cell divides into two is an example of information being carried through a cell lineage. Passing an environmentally influenced state from parent to child through eggs or sperm is a separate question.

Reproductive cells undergo extensive epigenetic remodeling. Studies in mice have mapped large-scale removal of DNA methylation during the development of cells that give rise to eggs and sperm. A proposed inherited mechanism must account for such remodeling.[11]

Exposure also needs to be counted carefully. During pregnancy, an exposure can affect the pregnant person, the developing fetus, and the fetus's developing reproductive cells. Effects in more than one generation do not automatically demonstrate transmission to an unexposed generation.

Families additionally share DNA sequences, foods, living conditions, and social experiences. Separating those influences from inheritance through an epigenetic mechanism is demanding work. Back at the table, the child has dropped the spoon.

You retrieve it and wipe up a little oatmeal. During these few minutes, countless signals have appeared, acted, and begun to fade. Some will influence the next few minutes. Others will contribute to processes unfolding over hours or days. Development adds possibilities that are particular to this stage of the child's life, while your own tissues continue to adjust within the capacities of adulthood.

That is the practical meaning of biological memory: history can alter how a system receives its next message.

The next chapter brings that understanding back to the table, asking what the evidence allows us to say about food choices—and how to make useful sense of a science in which the meal, the person, and the timing all matter.

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# Chapter 8: What the Science Means at the Table

You are back in the kitchen.

The oats are in the cupboard. There is yogurt in the refrigerator, fruit in a bowl, and a bag of frozen berries behind the peas. Somewhere on your phone, an advertisement promises a supplement that will transform your microbiome. Another headline claims that a particular food can switch off inflammation.

The mechanisms we have followed help explain both the appeal of these claims and the questions they leave unanswered. Now comes the practical question: how should this knowledge influence what you eat?

The starting point is reassuringly ordinary. Build meals that provide enough nourishment, include a variety of foods, suit your circumstances, and work reasonably well for your digestion. Let the emerging science refine that foundation as evidence develops.

A useful dietary choice does not require a complete molecular explanation. At the same time, a compelling molecular explanation does not, by itself, establish a useful dietary choice.

A change in microbial composition, an inflammatory marker, or a DNA methylation measurement is a biological finding. Its practical meaning depends on what it predicts or accompanies.

When evaluating a claim, look for the outcome actually measured. Better digestion, fewer symptoms, and improved daily functioning are different outcomes from a change in a laboratory measurement.

For everyday eating, the broad foundation is better established than the details of how particular foods influence brain epigenetics. Current World Health Organization guidance emphasizes fruits, vegetables, whole grains, pulses such as beans and lentils, and a varied diet that meets nutritional needs. It also recommends limiting free sugars, excess sodium, and less healthy fats. Frozen and canned fruits and vegetables can contribute alongside fresh foods.[1]

A meal might center on rice and beans, lentil soup, vegetables with tofu, or fish with potatoes. Whole grains might mean oats, wholemeal bread, millet, or another familiar staple. The ingredients do not need to come from a special “gut health” section of the shop.

Start with foods you already recognize and meals you already know how to prepare. A familiar dinner with an added vegetable or a portion of beans may be easier to repeat than an entirely new menu.

Repetition matters practically because food choices happen under constraints. Time, money, cooking facilities, appetite, disability, family responsibilities, and access all influence what reaches the table. Fiber connects ordinary nutrition with several mechanisms explored in this book. Different fibers can be fermented, contribute to stool bulk, or affect how water is held in the digestive tract. Foods supply different mixtures.

The WHO recommends that adults aim for at least 25 grams of naturally occurring dietary fiber from foods each day. This provides a population-level reference point; individual needs and medical circumstances can differ.[1]

You can move toward a higher-fiber pattern through ordinary changes: oats at breakfast, lentils added to soup, wholegrain bread, an apple, or vegetables alongside dinner. If your usual diet contains little fiber, abruptly adding large quantities can cause gas and discomfort. The National Institute of Diabetes and Digestive and Kidney Diseases advises gradual increases for people with irritable bowel syndrome and notes that soluble fiber may be more helpful for IBS symptoms than insoluble fiber.[2]

A modest serving that you tolerate is a reasonable place to begin. You can increase it as appropriate rather than treating the largest possible portion as the best one.

Gas or bloating tells you about comfort and tolerance. It does not measure butyrate production, an epigenetic change, or improved communication with the brain. Over time, try different vegetables, fruits, grains, pulses, nuts, or seeds that you enjoy and tolerate. Variety offers different combinations of nutrients and food components. It does not require an exotic ingredient every day or a precise weekly number that guarantees an ideal microbiome.

You might rotate two or three breakfasts, keep a few dependable dinners, and introduce something different when it is convenient. A varied pattern can develop through small choices across a week.

A bowl of vegetables alone may not make a satisfying meal. Include foods that supply energy and protein, along with appropriate sources of fat. Beans, lentils, tofu, eggs, fish, meat, dairy foods, and suitable alternatives can play different roles according to preference and need. General dietary guidance includes these alongside starchy foods, fruits, and vegetables.[3]

That might be wholegrain toast with eggs and tomatoes. It might be a bean filling in a tortilla, leftover chicken with rice and frozen vegetables, or tofu added to noodles and greens. Our familiar oatmeal can be accompanied by yogurt, nuts, or another food that makes breakfast sufficient for you.

Convenience can help. Frozen vegetables, canned beans, ready-cooked grains, and other prepared ingredients can make a workable meal possible on a difficult day.

A small trial in healthy adults compared diets emphasizing fermented foods with diets emphasizing fiber. The fermented-food group showed increased microbial diversity and reductions in several inflammatory markers. The fiber group showed increased microbial capacity to process complex carbohydrates, while immune responses varied and the main immune response measure did not improve across the group. These findings show that diets can influence measurable microbial and immune features; they do not establish that yogurt treats anxiety or produces a beneficial epigenetic change in the brain.[4]

If you enjoy a fermented food and tolerate it, it can have a place at the table. The evidence does not make fermented foods compulsory. “Fermented” and “probiotic” also describe different things. Fermentation involves microbial activity during food production. A probiotic claim

concerns live microorganisms with demonstrated benefits when consumed in an appropriate amount. A fermented food may not contain live microbes when you eat it, and the presence of live microbes alone does not establish a particular health benefit.[5]

Labels can help answer practical questions. Check the ingredients, whether live cultures are identified, and the amounts of added sugar or sodium. Choose a product for its overall fit in your diet, as well as for its taste.

The same discipline applies to probiotic supplements. Evidence about one strain, dose, and health condition cannot simply be transferred to a different product. A larger number of organisms on the label does not establish a larger benefit.

A food can be nutritious and still be uncomfortable for a particular person in a particular amount. Tolerance may differ with portion size, preparation, and the rest of the meal.

For some people with IBS, a structured low-FODMAP approach can help identify carbohydrates that contribute to symptoms. The approach includes a limited restriction phase, reintroduction, and personalization. Professional guidance does not describe permanent avoidance of every high-FODMAP food as the goal.[6]

A dietitian with relevant experience can help preserve nutritional adequacy while making those adjustments. Diagnosed conditions such as celiac disease, food allergy, and inflammatory bowel disease also require advice suited to the condition and the individual.

There are reasons to investigate whether improving diet can support mental health, and some human trials have reported encouraging results. In the SMILES trial, 67 adults with major depression were assigned to dietary support or a social support comparison group over twelve weeks. The dietary support group showed greater improvement in depressive symptoms. Most participants were also receiving psychotherapy, medication, or both.[7]

This was a small trial of an overall dietary support program. It did not identify a single antidepressant food or establish that microbial changes caused the improvement.

Other nutritional interventions have produced different results. The larger MooDFOOD trial followed more than a thousand adults with elevated depressive symptoms who did not have a recent episode of major depression. Neither its multinutrient supplement nor its food-related behavioral program reduced the onset of major depression over a year in the main analysis.[8]

These studies asked different questions about different interventions and populations. Together, they show why “food affects mood” is too broad to serve as a treatment instruction. Diet can be considered as part of care. Persistent depression or anxiety deserves appropriate assessment and treatment, and dietary changes should complement that care rather than replace it.

There is also a practical kindness in recognizing that illness can make food preparation difficult. On some days, the useful intervention may be a simple available meal, help with shopping, or food prepared by someone else.

The previous chapter showed that changing meal timing can shift some biological rhythms. That finding does not establish one correct eating window for every person, or prove that a particular fasting schedule improves the gut–brain axis.[9]

For practical purposes, look for opportunities to eat that fit your work, sleep, appetite, and medical needs. A dependable routine may make it easier to obtain adequate meals. Its usefulness does not depend on hitting an exact minute.

Supplements have clear uses for specific nutritional needs. A deficiency, a life stage, a medical condition, or a restricted diet may create a reason to use one. Taking more than needed, however, can add cost and increase the risk of adverse effects.[10]

Knowing that a nutrient participates in methylation does not tell us that a higher dose will improve gene regulation. Methylation has different consequences at different locations, and cells regulate the availability and use of these chemical materials.

Similarly, a laboratory finding that a compound influences a histone-modifying enzyme cannot determine an effective or safe supplement dose for people. A useful supplement recommendation should identify the need it addresses, the evidence for that use, and the appropriate amount. A promise to “optimize your epigenome” leaves those questions unanswered.

Sequencing microbes in a stool sample can generate detailed information. The harder task is showing that a particular interpretation leads to better decisions and better health. An international expert consensus concluded that evidence remains insufficient to recommend routine microbiome testing widely in clinical practice.[11]

You do not need a commercial microbial score before adding a tolerable portion of vegetables or choosing a wholegrain food. These commercial profiles are also distinct from established medical stool tests used to investigate particular illnesses.

Choose one change that addresses something real in your current routine. Perhaps breakfast leaves you hungry, vegetables rarely appear at dinner, or the only available lunch requires more preparation than you have time for.

Make the change concrete. Keep an easy protein food available. Add a small portion of beans to a familiar dish. Put frozen vegetables where you will remember them. Choose a fruit you like and can afford.

Notice whether the change satisfies you, feels comfortable to digest, and fits your resources. Those observations can help decide whether to keep it. If brief notes help identify a repeated pattern, use them. An ordinary observation can guide a practical adjustment without proving a biological mechanism. A better afternoon after a different lunch does not reveal which microbial molecule changed, and one uncomfortable evening does not identify the last food eaten as the cause.

The aim is to develop a pattern you can live with, including meals shared with others, foods chosen for pleasure, and days when convenience takes priority. You return the phone to the counter. Breakfast is still there.

You might add the berries, stir in yogurt, or choose something different that suits the morning. The meal can nourish you without carrying a promise to repair every pathway we have explored. You have enough information to make a thoughtful next choice, and room to adjust as you learn what works.

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# Conclusion

The bowl is empty. The spoon rests against its edge. You get up from the table and turn toward the rest of the day.

The meal continues. As digestion proceeds, nutrients become available to your cells. Materials that reach the large intestine enter the activities of its microbial communities. Molecules are produced, absorbed, transformed, and used. Signals help coordinate the work.

We began with this familiar event because it connects many levels of biology. Food supplies energy and building materials; microbes transform some of those materials; nerves, hormones, and immune signals carry influence between tissues. Within cells, responses can reach the machinery that regulates gene activity.

One central lesson runs through the whole journey: a biological effect depends on the encounter between a signal and a receiving system. A molecule does not act in isolation. Its concentration matters, as do its location, timing, and duration. The receiving cell brings its own receptors, metabolic needs, and regulatory state. Other signals may reinforce its response or restrain it.

The same principle applies at larger scales. Food enters a body that has been sleeping or working, resting or responding to illness. It encounters microbes whose activities depend partly on what has arrived before. It becomes one influence among many.

This helps explain why a mechanism can be convincing while a practical recommendation remains uncertain. Knowing that a molecule can influence an enzyme is an important discovery. Establishing that a particular meal produces a useful effect in people requires further evidence.

Gut microbes expand the range of chemical transformations that occur during digestion. Their products can nourish cells, interact with receptors, and influence immune activity or gene regulation. At the same time, the body shapes the environment in which microbes live.

A microbial community can change because its food supply changes or because the body changes its environment. The inflammation experiments in Chapter 6 showed one concrete example: a host response altered the conditions for bacterial growth. A different microbial profile is a finding to interpret, rather than a complete explanation of health.[1]

DNA provides genetic information, while its packaging and associated chemical marks help regulate how cells use it. Nutrients, metabolism, and signaling can influence parts of this machinery.[2]

Some changes are temporary. Some cellular states persist. Maintaining a state may require active work as cells grow, divide, and replace their components. More methylation is not automatically better. Greater activity of a gene is not automatically healthier. The meaning depends on which gene, which cell, and which circumstances.

An exposure during development may influence a system while it acquires its structure or patterns of responsiveness. The mouse weaning studies gave one example of an early microbial interaction influencing later immune responses.[3]

Yet finding a lasting effect does not establish that every aspect of a person's future has been determined. Nor does recognizing the possibility of change mean that every past effect can be erased.

At the table, the broad foundation remains a pattern that provides enough nourishment and includes foods you enjoy, can obtain, and tolerate. A variety of vegetables, fruits, grains, pulses, and other foods suited to your needs can contribute to it.[4]

Convenience belongs in this picture. Frozen vegetables, canned beans, simple sandwiches, leftovers, and meals prepared by someone else can all help turn an intention into something you can actually eat.

A workable eating pattern must also make room for individual needs. Digestive symptoms, allergies, medical conditions, and particular nutritional requirements can change what is appropriate. General advice becomes more useful when it is adapted thoughtfully. Persistent difficulties deserve attention even when someone is already eating carefully.

The gut–brain axis also broadens our understanding of symptoms. Stress can influence digestive function, while experimentally stimulated immune activity can alter emotional experience. These physical processes offer routes for investigation and care.[5,6]

They do not make illness a failure of attitude, discipline, or food choice. Understanding these mechanisms can make us more curious about food while keeping the influence of any one meal in proportion.

The body is continually responding, maintaining, repairing, and adjusting. Meals contribute to that work. Across time, they become part of a pattern of nourishment shaped by both choice and circumstance.

There will be more discoveries. Researchers will identify new signals, clarify existing pathways, and test which findings can improve people's lives. Some promising ideas will become useful practices. Others will remain limited to particular experimental settings.

You return to the kitchen later in the day. There is something to prepare, someone to feed, or simply a moment to sit down. A meal becomes a message.

Your task is to find nourishing, workable ways to keep eating across the life you actually live.

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# Glossary

Use this alphabetical guide whenever an unfamiliar word interrupts the story. The definitions focus on how each term is used in this book. For the experiments behind these ideas, return to the references at the end of each chapter.

**Acetate.** One of the short-chain fatty acids that gut microbes produce during fermentation. It can be used in the body's metabolism and can participate in signaling through receptors.

**Acetylation.** The attachment of a small chemical unit called an acetyl group to a molecule. Adding acetyl groups to histones can change DNA packaging and help other proteins recognize particular regions of chromatin.

**Acetyl-CoA.** A molecule that carries acetyl groups through many reactions inside cells. It connects the processing of nutrients with activities such as energy production and the supply of acetyl groups for histones.

**ACTH.** Short for adrenocorticotropic hormone. Released by the pituitary gland, it tells the adrenal glands to make cortisol. It is one step in the hormonal relay called the HPA axis.

**Amino acid.** One of the building blocks of proteins. Amino acids can also enter other chemical pathways. Tryptophan and methionine are two examples followed through the book.

**Aryl hydrocarbon receptor (AHR).** A protein inside cells that responds to certain molecules, including some products of microbial tryptophan metabolism. When activated, it works with other proteins to influence gene transcription.

**Association and causation.** An association means that two things vary together. Causation means that one helps produce the other. Finding a particular microbial pattern alongside illness does not, by itself, show that the microbes caused the illness.

**Astrocyte.** A type of cell in the brain and spinal cord that helps maintain the conditions neurons need. Astrocytes also take part in responses to injury and inflammation.

**Autonomic nervous system.** The parts of the nervous system that help regulate internal functions such as digestion, heart rate, and gland activity without requiring conscious direction. These pathways help the brain adjust digestive activity to changing circumstances.

**BCG vaccine.** A vaccine developed against tuberculosis. The study discussed in Chapter 7 also used vaccination to investigate whether an immune encounter could change later responses through effects on blood cells and the cells that produce them.

**Bile acids.** Molecules made from cholesterol in the liver that help the body digest and absorb fats. Gut microbes modify some bile acids. The resulting molecules can also interact with receptors and other proteins involved in signaling.

**Biological memory.** A lasting influence of an earlier experience on a later response or state. It can involve gene regulation, the makeup of a tissue, or other continuing changes. It does not require conscious remembering.

**Bromodomain.** A region of certain proteins that recognizes acetylated sites on histones. It is one example of a molecular “reader”: a protein feature that detects a chemical mark and helps connect it to other cellular machinery.

**Butyrate.** A short-chain fatty acid produced by some gut microbes. Many cells lining the colon use it as fuel. Depending on its concentration and the receiving cell, it can also influence receptors and enzymes involved in gene regulation.

**Cell differentiation.** The process through which a cell develops a more specialized identity and job. Changing patterns of gene activity help a developing cell become, for example, an intestinal lining cell or a neuron.

**Cholecystokinin (CCK).** A gut hormone released in response to food, particularly fat and protein. It helps coordinate digestion and contributes to signals of fullness.

**Choline.** A nutrient used to make cell membranes and the chemical messenger acetylcholine. Some choline can also be converted into betaine, which contributes to the network of reactions that supplies methyl groups.

**Chromatin.** DNA together with the proteins associated with it, including histones. This is the physical form in which genetic information is organized inside the nucleus. Its arrangement helps regulate access to DNA.

**Chromatin remodeling.** The rearrangement of DNA’s packaging by molecular machines that use energy. Moving or reorganizing nucleosomes can make a region of DNA easier or harder for other proteins to reach.

**Circadian rhythm.** A biological rhythm that repeats on an approximately twenty-four-hour cycle. Interacting clocks in the brain and other tissues help organize the timing of processes such as hormone release and nutrient handling.

**Colon.** The main portion of the large intestine. Many gut microbes live here, where they can use food components that escaped digestion earlier in the digestive tract.

**Cortisol.** A hormone made by the adrenal glands that helps regulate metabolism, immune activity, and responses to stress. Its effects depend on the receiving tissue, the amount present, and the pattern of exposure.

**CpG site.** A location along a DNA strand where the base cytosine, represented by C, is followed by guanine, represented by G. In mammals, many DNA methylation marks occur on the cytosine at these sites.

**CRH.** Short for corticotropin-releasing hormone. In the HPA axis, the hypothalamus releases CRH to stimulate the pituitary gland to release ACTH, beginning a relay that leads to cortisol production.

**CRISPR-based epigenome editing.** A laboratory approach that uses an adapted DNA-targeting system to bring gene-regulating proteins to chosen places in the genome without cutting the DNA. CRISPRoff, described in Chapter 4, is a tool for establishing gene repression with epigenetic modifications.

**Cross-feeding.** The use of one microbe's products by another microbe. In the microbial kitchen, one organism may break down an ingredient that another can then use.

**Crypt.** A small pocket in the intestinal lining. In the colon, cells near the base help renew the lining, while more mature cells nearer the contents of the gut can influence which molecules reach them.

**Cytokine.** A small protein that carries messages between cells, especially during immune responses. Different cytokines can encourage, redirect, or restrain a response. Their effects depend on which cells receive them and what else is happening.

**DNA.** Short for deoxyribonucleic acid. This molecule stores genetic information in the order of its chemical building blocks, represented by A, C, G, and T. Most of a human cell's DNA is kept in its nucleus.

**DNA methylation.** The attachment of methyl groups to DNA. Methylation in some gene-control regions can help reduce transcription, but its meaning depends on location. A higher overall amount is not a general measure of better health.

**Endotoxin.** A component of the outer membrane of certain bacteria that can stimulate immune responses. Researchers sometimes use a carefully controlled dose to study inflammation. Such experiments are different from the exposures involved in ordinary digestion.

**Enhancer.** A stretch of DNA where regulatory proteins can help increase a gene's transcription. An enhancer can act from some distance away along the DNA sequence.

**Enteric glia.** Supporting cells in the gut's nervous system. They help maintain the environment around neurons and communicate with other cells, including cells involved in immune responses.

**Enteric nervous system.** The network of neurons and supporting cells within the digestive tract. It helps coordinate movement and secretions locally and communicates with the brain and spinal cord.

**Enzyme.** A molecule, usually a protein, that speeds up a chemical reaction. Digestive enzymes break down food; other enzymes build molecules, transform microbial products, or add and remove chemical marks on chromatin.

**Epigenetic inheritance.** The passing on of a gene-regulating state without changing the DNA sequence. Maintenance through cell division and transmission from parent to offspring are different processes. Evidence for one does not establish the other.

**Epigenetic mark.** A chemical modification to DNA or its associated proteins that can help influence gene regulation. A mark may help establish or maintain a state, but its presence alone does not prove that it caused a change in gene activity.

**Epigenetics.** The study of how DNA packaging and associated chemical modifications help regulate gene activity while the DNA letter sequence stays the same. Some regulatory states are maintained through cell division; others change as conditions change.

**Epigenome.** The overall pattern of epigenetic modifications in a cell. Different types of cells can have different epigenomes even though they carry essentially the same DNA sequence.

**Epithelial cell.** A cell that forms part of a tissue's covering or lining. Intestinal epithelial cells help absorb nutrients and manage contact between the body and the contents of the gut.

**Feedback loop.** A process in which a response returns to influence the activity that produced it. Negative feedback restrains a change; positive feedback reinforces it. The words describe direction, rather than whether the result is beneficial.

**Fermentation.** A way microbes obtain energy by transforming available materials. In the colon, fermentation of certain carbohydrates produces compounds such as short-chain fatty acids. Food fermentation, as in yogurt production, happens before the food is eaten.

**Fiber.** Food components, mainly carbohydrates, that resist digestion by our own digestive enzymes. Different fibers behave differently: some are readily fermented by microbes, while others contribute more to stool bulk or water retention.

**FODMAPs.** An abbreviation for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. These are groups of carbohydrates that can contribute to digestive symptoms in some people. A low-FODMAP approach is a structured way to investigate tolerance, with reintroduction following a limited restriction phase.

**Folate.** A B vitamin involved in transferring small units containing one carbon atom. It helps support the metabolic network that supplies materials for DNA production and methylation reactions.

**Gene.** A region of DNA containing information used to make a functional RNA molecule or, through RNA, a protein. A cell carries many genes but uses them in different amounts and at different times.

**Gene expression.** The use of a gene's information to produce RNA and, for protein-coding genes, protein. A gene's activity can rise or fall; expression is more varied than a simple on-or-off switch.

**Gene regulation.** The processes that control when, where, and how much a gene is used. Regulation includes the actions of transcription factors, DNA packaging, chemical modifications, and other controls. A change in expression does not necessarily establish lasting epigenetic memory.

**Germ-free animal.** An animal raised under special laboratory conditions without a microbiota. These animals help researchers investigate what microbes contribute, but their unusual development limits how directly findings can be applied to people.

**GLP-1.** Short for glucagon-like peptide-1. A hormone released by certain gut cells that helps regulate blood glucose and appetite. It is one of several signals involved in the body's response to a meal.

**Glucocorticoid.** A member of a family of hormones that includes cortisol. Glucocorticoids influence metabolism, immune activity, and gene regulation. Their effects can differ across tissues and patterns of exposure.

**Gut–brain axis.** The interacting routes through which the digestive system and brain influence each other. These include nerves, hormones, immune signals, and microbial products. The term describes an exchange in both directions.

**Histone.** A protein that helps package DNA. DNA winds around groups of histones to form nucleosomes. Chemical modifications on histones can alter their interactions with DNA and with other regulatory proteins.

**Histone deacetylase (HDAC).** An enzyme that removes acetyl groups from histones and sometimes other proteins. By changing these chemical attachments, HDACs can influence gene regulation. HDAC3 is one member of this enzyme family.

**Hormone.** A chemical messenger released by cells that can travel through the bloodstream and affect cells with suitable receptors. Gut hormones and stress hormones help coordinate activity across different parts of the body.

**Host.** The organism in or on which microbes live. In this book, a "host cell" usually means a cell belonging to the person or research animal, rather than to one of its microbes.

**HPA axis.** Short for hypothalamic–pituitary–adrenal axis. This hormonal relay connects a brain region, the pituitary gland, and the adrenal glands. It helps regulate cortisol production, with feedback that adjusts further hormone release.

**Immune system.** The network of cells, tissues, and signals that helps defend the body and respond to damage. In the gut, it must also manage contact with food and resident microbes while limiting unnecessary inflammation.

**Inflammation.** A coordinated response to threats or tissue damage that involves immune cells and chemical signals. It can support defense and repair, but its persistence or poor regulation can contribute to harm. Digestive discomfort alone does not demonstrate inflammation.

**Intestinal barrier.** The structures and processes that manage what passes between the gut's contents and the body. The intestinal lining, junctions between cells, and mucus all contribute. A functioning barrier permits absorption while limiting inappropriate contact.

**Intestinal permeability.** How readily a particular substance crosses the intestinal barrier under particular conditions. The result depends on what is measured and where. Passage of a small test molecule does not by itself show that bacteria are entering the bloodstream.

**Macrophage.** An immune cell that can engulf microbes, debris, and dying cells. Macrophages also release signals that influence inflammation and repair. What they encounter helps shape how they respond.

**Metabolism.** The network of chemical reactions that keeps a cell or organism functioning. It includes breaking materials down, releasing energy, and building or recycling molecules.

**Metabolite.** A substance produced or used during metabolism. Butyrate, for example, is a microbial metabolite that our cells may use as fuel or encounter as a signal. The word does not imply a health benefit.

**Methionine.** An amino acid used to build proteins and to make SAM, an important donor of methyl groups. Its role in methylation links nutrient processing with some forms of gene regulation.

**Methylation.** The attachment of a methyl group, a unit containing one carbon and three hydrogen atoms, to another molecule. DNA methylation and histone methylation occur on different materials. Their consequences depend on the site and surrounding regulatory machinery.

**Microbe.** A microscopic organism, such as a bacterium or yeast. Many microbes live in and on the body. Their activities depend on their surroundings and on the materials they can use.

**Microbiome.** A term used for a microbial community, often including its collective genes, activities, and environment. Usage varies between studies. In this book, it helps us look beyond which organisms are present to what their community can do.

**Microbiota.** The microorganisms living in a particular place, such as the gut. The term focuses on the inhabitants themselves. Their names alone do not reveal which chemical pathways are active.

**Neuron.** A nerve cell that receives and passes on information. Traveling electrical changes carry signals along the cell, and chemical messengers often carry them across connections to other cells.

**Neurotransmitter.** A chemical messenger released by a neuron to influence another cell across a connection. Glutamate is one example. Some other kinds of cells can use the same messenger molecules to communicate with nerves.

**Nucleosome.** A basic unit of DNA packaging: a length of DNA wrapped around a core of histone proteins. The spool-and-thread comparison helps picture its structure, although it is a changing molecular assembly.

**One-carbon metabolism.** A network of reactions that transfers small units containing one carbon atom. Nutrients including folate, vitamin B12, choline, and methionine participate in connected parts of this network, which helps supply methylation reactions.

**Probiotic.** A live microorganism shown to provide a health benefit when consumed in an appropriate amount. The relevant organism, amount, and benefit matter. A fermented food or a product containing live microbes is not automatically a proven probiotic.

**Promoter.** A region of DNA near the beginning of a gene where proteins help organize the start of transcription. Its accessibility and the proteins gathered there influence how readily the gene is read.

**Propionate.** One of the short-chain fatty acids produced by gut microbes. Like acetate and butyrate, it can enter metabolic pathways and interact with signaling systems, but the three compounds are handled differently by the body.

**Protein.** A molecule built from amino acids and folded into a shape that enables it to work. Proteins serve as enzymes, receptors, structural components, and many other parts of cellular machinery.

**Randomized controlled trial.** A study that assigns participants by chance to an intervention or a comparison group. This helps researchers assess whether the intervention caused a difference. The conclusion still depends on the people studied, the comparison, and the outcome measured.

**Receptor.** A protein that detects particular molecules or other signals and helps trigger a response. Some receptors sit on a cell's surface; others act inside it. The receiving cell's equipment shapes what happens next.

**Regulatory T cell.** A type of immune cell that helps restrain other immune responses. These cells contribute to controlling inflammation and tolerating many of the substances the body normally encounters.

**Resistant starch.** Starch that escapes digestion in the small intestine and can become available to microbes farther along the gut. Whether and how it is used depends partly on its structure and the microbial community present.

**RNA.** Short for ribonucleic acid. Some RNA carries information copied from DNA to the machinery that makes proteins. Other RNA molecules have different jobs, including helping regulate genes or carry out cellular reactions.

**SAM and SAH.** SAM, short for S-adenosylmethionine, supplies methyl groups for many reactions. After donating a group, it becomes SAH, or S-adenosylhomocysteine. SAH can inhibit methylating enzymes, so both supply and removal of reaction products matter.

**Sensitive period.** A stage of development when a particular experience can have an especially strong influence on a system. Different tissues have different sensitive periods. The term does not mean that every later response is permanently fixed.

**Short-chain fatty acids (SCFAs).** Small fatty acids produced when gut microbes ferment certain materials, including some fibers. Acetate, propionate, and butyrate are major examples. They can supply energy and influence signaling, with effects that depend on where they go and which cells encounter them.

**Signaling.** The process through which cells detect information and change their activity. A message can change form along the way: a molecule may activate a receptor, trigger electrical activity, or prompt another cell to release a hormone.

**Stem cell.** A cell that can renew itself and produce cells that develop more specialized roles. Stem cells in intestinal crypts help replace cells in the gut lining.

**TET enzymes.** Enzymes that chemically alter methylated cytosine in DNA. Their reactions can begin processes that lead to removal of DNA methylation. Vitamin C can support their activity under the conditions explored in Chapter 5.

**Trained immunity.** A lasting change in the responsiveness of certain immune cells after an earlier encounter. Changes in metabolism and gene regulation can help carry the effect forward. A stronger later response is not necessarily beneficial in every setting.

**Transcription.** The copying of information from DNA into RNA. For a protein-coding gene, this is an early step toward making protein. Transcription also produces RNAs that carry out jobs of their own.

**Transcription factor.** A protein that helps control transcription by interacting with particular DNA sequences and other regulatory proteins. Signals can change its activity, connecting events outside the nucleus with the use of genes inside it.

**Translation.** The process in which ribosomes, the cell's protein-building machinery, use the information in messenger RNA to assemble amino acids into a protein.

**Tryptophan.** An amino acid used in protein production and other pathways. Gut microbes can transform some tryptophan into compounds that interact with host cells, including molecules that act through AHR.

**Vagus nerve.** A major bundle of nerve fibers connecting the brain with internal organs, including parts of the digestive tract. Sensory fibers carry information toward the brain; other fibers carry signals outward that help regulate organ activity.

**Writers, readers, and erasers.** A shorthand for proteins involved in epigenetic regulation. Writers add chemical marks, readers recognize them, and erasers remove or alter them. Their combined activity helps shape how a cell uses its genetic information.

## Further reading


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Food and the Gut–Brain Axis

# A meal is the beginning of a conversation.

Food does more than fuel the body. It enters a busy world of gut microbes, chemical signals, and cells responding to their surroundings.

Follow an ordinary meal as it becomes part of the conversation between gut and brain. Along the way, discover how microbes transform food, why stress and inflammation matter, and how epigenetics helps shape gene activity without rewriting DNA.

With everyday examples and simple diagrams, this book makes complex science approachable. Drawing on research while acknowledging what remains uncertain, it offers a balanced perspective on food choices and the remarkable biology behind them.



Martin J Coyne, MD, MMI