

## HEALTH

## The Fundamental Link Between Body Weight and the Immune System

Inflammation plays a critical role in determining how we digest food, and it's only now starting to reveal itself.

JAMES HAMBLIN AUG 2, 2019



EDGAR SU / REUTERS

It's simple: Eat less.

Sometimes combined with the directive *move more*, this mantra has a clear point. If you can't lose weight, you are either stupid or lazy—or, probably, both. See also: *Calories in, calories out*.

But if things were that simple, diets would work. Middle-aged people would not suddenly start gaining weight despite eating and moving similarly year after year. No one would have to endure the presence of that one friend with the “fast metabolism” who can eat anything he wants. And who, even though he knows you're on a diet, says through his overstuffed mouth, “I couldn't even gain weight if I tried.”

Instead, it is becoming clear that some people's guts are simply more efficient than others' at extracting calories from food. When two people eat the same 3,000-calorie pizza, for example, their bodies absorb different amounts of energy. And those calorie-converting abilities can change over a person's lifetime with age and other variables.

The question is, why? And is it possible to make changes, if a person wanted to?

If so, the solution will involve the trillions of microbes in our intestines and how they work in concert with another variable that's just beginning to get attention. The immune system determines levels of inflammation in the gut that are constantly shaping the way we digest food—how many calories get absorbed, and how many nutrients simply pass through.

The relationship between microbes and weight gain has long been overlooked in humans, but people have known about similar effects in animals for decades. After World War II, antibiotics became affordable and abundant for the first time. Farmers began giving the drugs to their livestock—for example, to treat a milk cow's infected udder—and noticed that animals who got antibiotics grew larger and more quickly.

This led to a flood of patent applications for antibiotic-laden foods for all sorts of livestock. In 1950, the drug company Merck filed a patent for “a method of accelerating the growth of animals” with “a novel growth-promoting factor” that was, simply, penicillin. Eli Lilly patented three new antibiotics to mix into the feed of sheep, goats, and cattle because the microbe-killing agents “increased feed efficiency.” In the ensuing decades it became standard practice to give livestock copious doses of antibiotics to make them grow faster and larger, even though no one knew why this happened, or what other effects the practice might have.

*[ Read: Are antibiotics making people larger? ]*

Researchers have only recently shown that these antibiotics kill off some of the microbes that occur normally in the gut and help livestock, and people, digest food. By breaking down nutrients and helping them pass through the walls of the bowel, these microbes serve as a sort of gatekeeper between what is eaten and what actually makes it into the body.

Killing them is not without consequences. Just as antibiotics are associated with faster growth in cattle, a decrease in diversity in the human microbiome is associated with obesity. As the usage of animal antibiotics exploded in the 20th century, so too did usage in humans. The rise coincides with the obesity epidemic. This could be a spurious correlation, of course—lots of things have been on the rise since the '50s. But dismissing it entirely would require ignoring a growing body of evidence that our metabolic health is inseparable from the health of our gut microbes.

In 2006, Jeffrey Gordon, a biologist at Washington University in St. Louis, reported that the microbiomes of obese mice had something in common: Compared with their lean counterparts, the heavier mice had fewer *Bacteroides* and more *Firmicutes* species in their guts. What's more, biochemical analyses showed that this ratio made the microbes better at “energy harvest”—essentially, extracting calories from food and passing it into the body. That is, even when mice ate the same amount and type of food, the bacterial populations meant that some developed metabolic problems, while others didn't. Similar bacterial patterns have since been confirmed in obese humans.

What's more, Gordon found, the microbiome associated with obesity is transferable. In 2013, his lab took gut bacteria from pairs of human twins in which only one twin was obese, then fed the samples to mice. The mice given bacteria from the obese humans quickly gained weight. The others did not.

Gut bacteria are also transferred between humans, in the form of fecal transplants, as an experimental treatment for serious infections like *Clostridium difficile*. In one study, obese patients who received transplants from lean donors later had healthier responses to insulin.

[ *Read: How obesity became a disease* ]

Short of this sort of hard reset of the microbiome, preliminary research has shown that adding even a single bacterial species to a person's gut can alter her metabolism. In a clinical trial reported last month in the journal *Nature Medicine*, people who took a probiotic containing *Akkermansia muciniphila*—which is typically found in greater amounts in non-obese people—saw subtle metabolic improvements, including weight loss.

The study authors are not suggesting that anyone go out and buy this bacterium. But they call it a “proof of concept” for the idea that it’s possible to change a person’s microbiome in ways that have metabolic benefits.

Because leanness and obesity seem to be transmissible through the microbiome, “metabolic disease turns out to be, in some ways, like an infectious disease,” says Lora Hooper, the chair of the immunology department at the University of Texas Southwestern Medical Center. Hooper did her postdoctoral research in Gordon’s lab in St. Louis. While other researchers focused on the gut microbiome itself, she took an interest in the immune system. Specifically, she wanted to know how an inflammatory response could influence these microscopic populations, and thus be related to weight gain.

Over the past decade or so, multiple studies have shown that obese adults mount less effective immune responses to vaccinations, and that both overweight and underweight people have elevated rates of infection. But these were long assumed to be effects of obesity, not causes.

“When I started my lab there wasn’t much known about how the immune system perceives the gut microbes,” Hooper says. “A lot of people thought the gut immune system might be sort of blind to them.” To her, it was obvious that this couldn’t be the case. The human gut is host to about 100 trillion bacteria. They serve vital metabolic functions, but can quickly kill a person if they get into the bloodstream. “So clearly the immune system has got to be involved in maintaining them,” she says. It made sense to her that even subtle changes in the functioning of the immune system could influence microbial populations—and, hence, weight gain and metabolism.

This theory was borne out late last month in a paper in *Science*. Zac Stephens, a microbial ecologist at the University of Utah, and his colleagues had been working with mice with altered immune T cells. They noticed that over time, these mice “ballooned,” as Stephens puts it. One of his colleagues started calling them “pancakes.”

To figure out how such an immune change could cause obesity, they tested the biomes of the mice with and without the immune alteration. They found that healthy mice have plenty of bacteria from a genus called *Clostridia*, but few from *Desulfovibrio*, and that their guts let most fat pass right through. Those with an

altered immune system had fewer *Clostridia* and more *Desulfovibrio*, and this microbial balance helped the gut absorb more fats from food. These mice gained more weight and exhibited signs of type 2 diabetes.

“Whether this applies in humans, we don't know,” Hooper says, “but this is a tantalizing clue.”

Mice are not humans, but their microbiomes are about as complex as our own. Reduced *Clostridia* and increased *Desulfovibrio* are seen in people with obesity and type 2 diabetes. Bacteria can reasonably be expected to function similarly in the guts of different species. But even if they don't, this experiment is a demonstration of principle: The immune system helps control the composition of the gut microbiome.

[ *Read: How the immune system controls social behavior* ]

It does so by regularly mounting low-level immune responses to keep populations of bacteria in check. “The gut is under a constant state of inflammation, so to speak—constant immune stimulation from all the microbes,” says Stephens, pushing back on the common misconception that inflammation is always bad. The role of the immune system in the gut is to maintain balance. Changes to the body's defenses, which can happen as a result of age or illness, can cause certain species to flourish at the expense of others.

This is the interesting part to Steven Lindemann, a researcher at Purdue University who was not involved in the Utah study. He studies the effects of foods on the gut microbiome. “Although we know that, on the balance, diet is the strongest contributor to gut microbiome composition,” he said, this study suggests that when immune control of the colon breaks down, growth can become unchecked and cause problems with metabolic regulation.

Lindemann says the fact that the immune system regulates the inhabitants of the small intestine is well established. He compares the bowel wall to a customs checkpoint: The goal is to weed out bad actors and illegal cargo, but allow legitimate trade to progress as rapidly as possible. In the case of the immune-altered mice, he says, “we have a colonic border patrol that is seemingly out to lunch, allowing bad actor *Desulfovibrio* to bloom.”

If similar microbial changes have comparable effects in humans, it could have far-reaching implications for our diets. The very ideas of “nutritional value” and “calorie content” of food seem to vary based on the microbial population of the person eating it and, potentially, her immune status. A person’s own microbes—and those contained in any given food—would have to be considered as another component of the already flimsy calories-in, calories-out equation. This would also compound the challenges already facing nutrition labels.

People trying to control their weight might conclude that tinkering with their own microbiomes is the solution. This stands to fuel the already dubious and barely regulated industry of “probiotic” supplements, which has been projected to grow to \$7 billion by 2025. But the answer probably won’t be so simple.

“A lot of the recent research on probiotics suggests it’s really not easy to keep and sustain new communities,” Stephens says. The immune system could explain that. “It may well be that your immune response gets ‘stuck’ at an early age based on what you’ve exposed it to. Probiotics might not be enough to change a person’s microbiome, because your immune system determined early on that certain microbes are either appropriate or inappropriate in your gut.”

*[ Read: At last, a big, successful trial of probiotics ]*

Stephens says the relationship between weight and the immune system is likely to get more complicated before it gets simpler. That makes it difficult to give concrete advice. “Keeping diverse gut microbes with diverse dietary sources is probably the safest advice for now,” he says. “That will stimulate a healthy, strong immune system that can learn and regulate and do all the things it does, in ways we’re just beginning to understand.”

If all this uncertainty makes nutrition guidelines and nutrition even more inscrutable, it also stands to do some good by undermining the moralizing and simplistic character judgments often associated with body weight. Seeing obesity as a manifestation of the interplay between many systems—genetic, microbial, environmental—invites the understanding that human physiology has changed along with our relationship to the species in and around us. As these new scientific models unfold, they impugn the idea of weight as an individual character flaw, revealing it for the self-destructive myth it has always been.

*We want to hear what you think about this article. Submit a letter to the editor or write to [letters@theatlantic.com](mailto:letters@theatlantic.com).*

---

## MARK THE NEWS AS READ

Get a roundup of the most important and intriguing stories from around the world, delivered to your inbox every weekday.

---

## THE VALUE OF GOOD JOURNALISM

Subscribe and support our coverage of the ideas that matter – with up to 78% savings.

**SUBSCRIBE >**

**ABOUT**

**CONTACT**

**PODCASTS**

**SUBSCRIPTION**

**FOLLOW**

[Privacy Policy](#) [Advertising Guidelines](#) [Terms Conditions](#) [Responsible Disclosure](#) [U.S. Edition](#) [World Edition](#) [Site Map](#)

TheAtlantic.com Copyright (c) 2019 by The Atlantic Monthly Group. All Rights Reserved.

