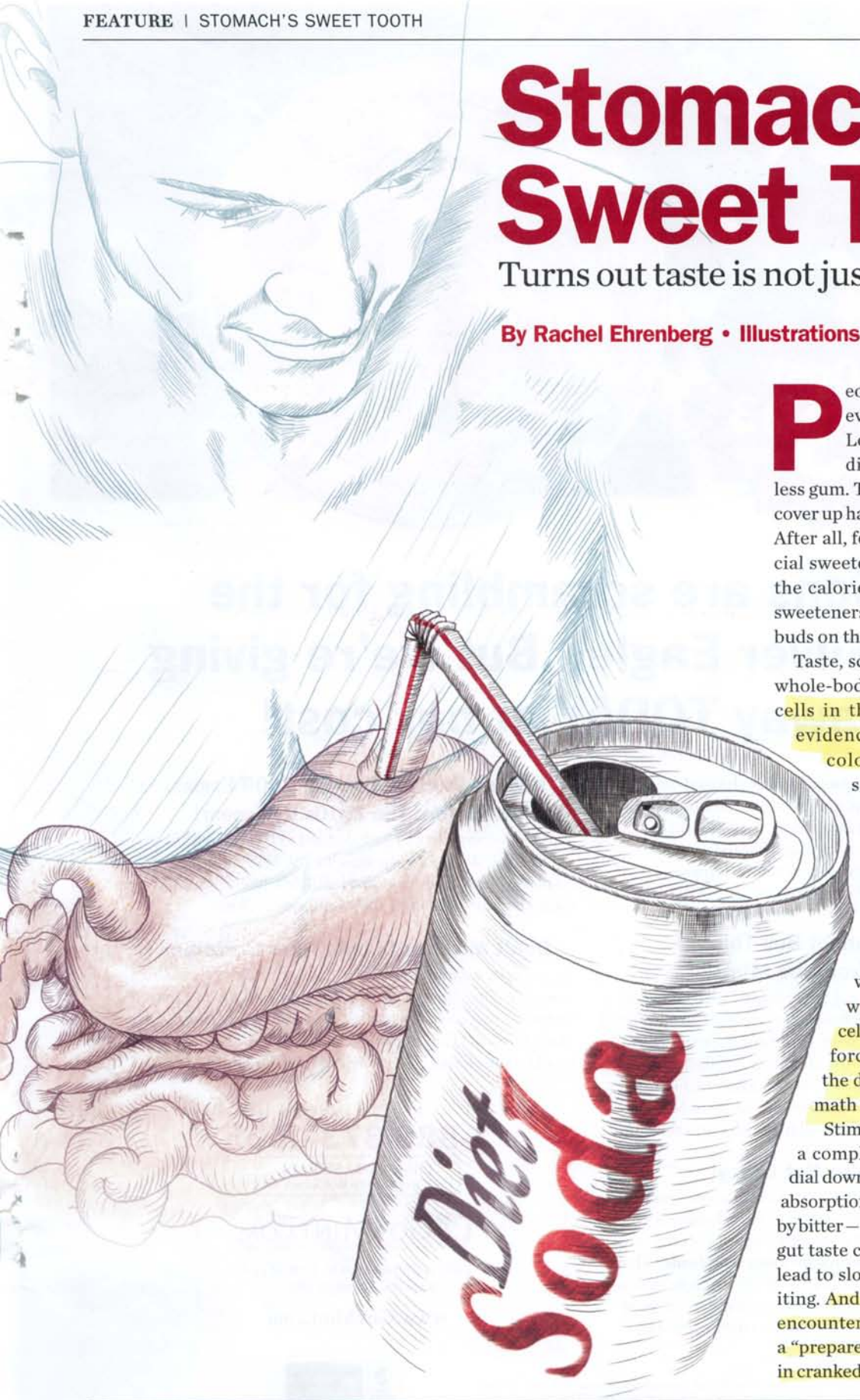
Stomach's Sweet Tooth

Turns out taste is not just for the tongue

By Rachel Ehrenberg • Illustrations by Nicolle Rager Fuller



People deceive their taste buds every day—a dash of Sweet'N Low in the coffee, perhaps, a diet soda or a stick of sugarless gum. These little white lies seem to cover up harmless, even healthy choices. After all, fooling the mouth with artificial sweeteners provides a fix without the calories or the cavities. But these sweeteners aren't just tricking the taste buds on the tongue.

Taste, scientists are discovering, is a whole-body sensation. There are taste cells in the stomach, intestine and, evidence suggests, the pancreas, colon and esophagus. These sensory cells are part of an ancient battalion tasked with guiding food choices since long before nutrition labels, Rachael Ray or even agriculture existed. While taste cells in the mouth make snap judgments about what should be let inside, new work suggests that gut taste cells serve as specialized ground forces, charged with preparing the digestive system for the aftermath of the tongue's decisions.

Stimulating these gut cells triggers a complex series of events that can dial down, or amp up, the digestion and absorption of the body's fuel. When hit by bitter—potentially toxic—substances, gut taste cells sound an alarm that may lead to slower absorption or spur vomiting. And when the gut's taste sensors encounter something sweet, they send a "prepare for fuel" missive that results in cranked-up insulin levels in the blood.

Though scientists don't fully understand what follows, studies hint at a tantalizing, if convoluted, connection between gut taste cell activity and metabolism. Figuring out such connections may one day lead to new therapies for treating type 2 diabetes, obesity and other disorders. And the sweet-focused research could help explain recent counterintuitive findings that link such problems with drinking diet soda.

Rumblings from the gut

The gut's taste cells appear to be built from the same machinery as the taste cells of the tongue, the structures of which scientists have only recently nailed down. Taste cells interact with what are called "tastants" via receptors, specialized proteins that protrude from cell walls and bind to specific molecules drifting by. When a tastant binds to a receptor, it signals other molecules that, in the mouth, immediately send an "accept" or "reject" message to the brain.

Bitter compounds activate a family of receptors called T2Rs—there are roughly 25 kinds in humans, a variety that reflects the importance of detecting potential toxins and avoiding lethal diet mistakes. But sweet tastes and savory ones, also called umami, appear to have one receptor each. Related proteins make up both receptors, a shared structure that makes evolutionary sense since the two detect valuable, energy-rich foods. The sweet receptor is built from two proteins, dubbed T1R2 and T1R3, while T1R3 combines with a different subunit to make the umami receptor.

A signaling molecule triggered by tongue taste receptors led scientists to the gut's sensors in the late 1990s. Researchers found gustducin, a protein that gets the message going when the mouth's sweet, bitter or umami receptors are hit, in some gut and pancreas cells in rats. Nearly 10 years later, scientists established that gut cells using gustducin were "tasting" too. A team including Robert Margolskee and Bedrich Mosinger, then at Mount Sinai School of Medicine in New York City, reported that taste receptors weren't just active in the rodent gut, but also in human intestinal cells.

In the mouth, stimulating sweet receptors sends a quick go-ahead to the brain, which rapidly sends more missives, ensuring that saliva is pumped and chewing and swallowing ensues. Sweet taste receptors in the gut seem to take this response to the next level, affirming that fuel is indeed incoming and setting off reactions to cope with it.

The gut isn't just a pit stop ... it is also a signaling station that keeps the body in tune with what's about to happen.

Gut taste cells appear to regulate, in part, secretion of insulin, a hormone crucial for telling body tissues whether they should tap newly arrived glucose or valuable stored fat for energy. Blocking sweet taste receptors in human intestinal cells grown in a lab dish reduced release of an important hormone, glucagon-like peptide-1, known to increase insulin secretion, Margolskee and Mosinger reported in 2007 in the *Proceedings of the National Academy of Sciences*. Mice without working gustducin also released less of the hormone. And the mice made less of a protein that helps with glucose absorption, suggesting that their bodies hadn't fully gotten the fuel-delivery message, the researchers, both now at the Monell Chemical Senses Center in Philadelphia, reported in a second paper in the same issue of the journal.

A dietary sugar and building block of carbohydrates and many dairy products, glucose is the fundamental fuel: The body metabolizes glucose to make ATP, the energy currency of cells. Fuel's a hot commodity, so it's fitting that taste cells in the gut prepare the body to take advantage of it when it's available, says Pankaj Jay Pasricha of Stanford University School of Medicine. If the body doesn't know glucose is there, cells can't exploit the molecule to move muscles, fire nerves or do any other basic body function.

The gut isn't just a pit stop where foods are made usable, he says; it is also a signaling station that keeps the body in tune with what's about to happen.

"It's not surprising," says Pasricha. "It's surprising that it took us so long to find out."

Answers from within

The discovery that gut taste cells play a role in that signaling system may help explain several persistent mysteries of metabolic science.

Scientists have long been puzzled by the fact that the pancreas releases far more insulin when a person ingests glucose than when it is injected directly into the blood. Known as the incretin effect (incretins are gut hormones that trigger insulin release), the response is thought to be due in part to glucagon-like peptide-1 activity. The link between taste cells in the gut and the release of GLP-1 may explain the effect, Pasricha and Stanford colleague Kelley Yan wrote

Ready, sweet, fire

A suite of compounds stimulates the mammalian sweet taste receptors on the tongue. Evidence now suggests that many of these same molecules activate taste receptors in the gut as well.

Sugars	Artificial sweeteners	D-amino acids	Sweet proteins
Examples: ▪ sucrose ▪ fructose ▪ glucose ▪ maltose	Examples: ▪ saccharin ▪ aspartame ▪ neotame ▪ sucralose	Examples: ▪ D-alanine ▪ D-phenylalanine ▪ D-serine	Examples: ▪ monellin ▪ curculin ▪ thaumatin
Found in: ▪ fruits ▪ milk ▪ pasta ▪ honey	Found in: ▪ candy ▪ breakfast bars ▪ canned fruits ▪ soft drinks	Found in: ▪ aged cheese ▪ aged meat	Found in: ▪ serendipity berry ▪ *Curculigo latifolia* berries ▪ *Thaumatococcus daniellii* berries

SOURCE: J. CHANDRASHEKAR *ET AL./NATURE* 2006

in a commentary in the July 2009 *Gut*. If the gut never tastes glucose because the sugar enters via an IV, the body might not prepare for the fuel delivery.

Taste-receptor cells in the gut may also be responsible for two odd side effects of existing medical treatments, some scientists have suggested.

Many people with type 2 diabetes are insulin resistant — meaning their tissues ignore the hormone's signal to absorb glucose from the blood, which may lead to dangerously high blood sugar levels. Some overweight patients who undergo gastric bypass surgery experience an almost instant decrease in insulin resistance, Pasricha notes. The surgery shortens the nutrient-absorbing portion of the small intestine. Some scientists think this could give taste cells at the tail end of the intestine — cells that may still function properly — a chance to ramp up local secretion of GLP-1 and restore normal metabolism.

The second case involves people with type 2 diabetes who take fibrates, drugs often used along with statins to treat high cholesterol. Side effects can include lower blood sugar levels, suggesting less insulin resistance.

Mosinger and colleagues noticed that fibrates are structurally similar to lactisole, a known blocker of sweet receptors. The researchers exposed mouse and human cells decked with sweet receptors to various concentrations of the compounds. Fibrates blocked sweet receptors in human cells but not in mouse cells, the team reported online in October in the *Journal of Medicinal Chemistry*. This blocking may somehow affect insulin resistance, Mosinger proposes.

"We are still in the stage of intense research," he cautions. Eventually such research may yield targets for new therapies: "Many people are hopeful that in the future there could be treatments."

Bitter taste receptors in the gut may also be good future drug targets, says Catia Sternini of the University of California, Los Angeles. In the mouth, these receptors send red-alert rejection signals, but gut bitter receptors seem to play a role in slowing or preventing the absorption of toxic compounds that make it past the tongue. "These bitter receptors could be seen as a second line of defense," Sternini says. "They help the gut distinguish the good from the bad. If there is a toxin, the response is to try to reduce damage."

The mechanisms still aren't clear, she says, but work suggests that activating gut bitter receptors can trigger reactions that convince a body that it's satiated.

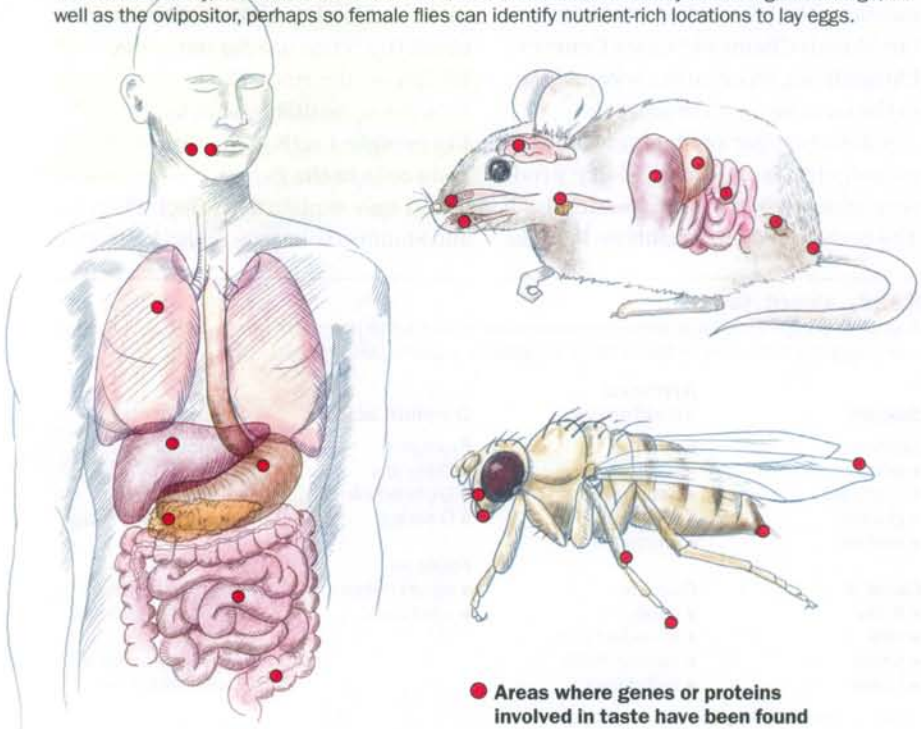
Scientists have only just begun to explore the sweet, umami and bitter receptors in the gut. Work on sour and salty receptors — assumed to also be present — has just begun. And taste cells represent a fraction of the gut's signaling system. Gut signaling cells make up less than 1 percent of the cells of the intestinal wall, yet together these signaling cells constitute the largest hormone-releasing organ of the body, Sternini pointed out in 2007 in *Current Opinion in Pharmacology*. "The gut," she says, "is an amazing organ."

Twists and turns

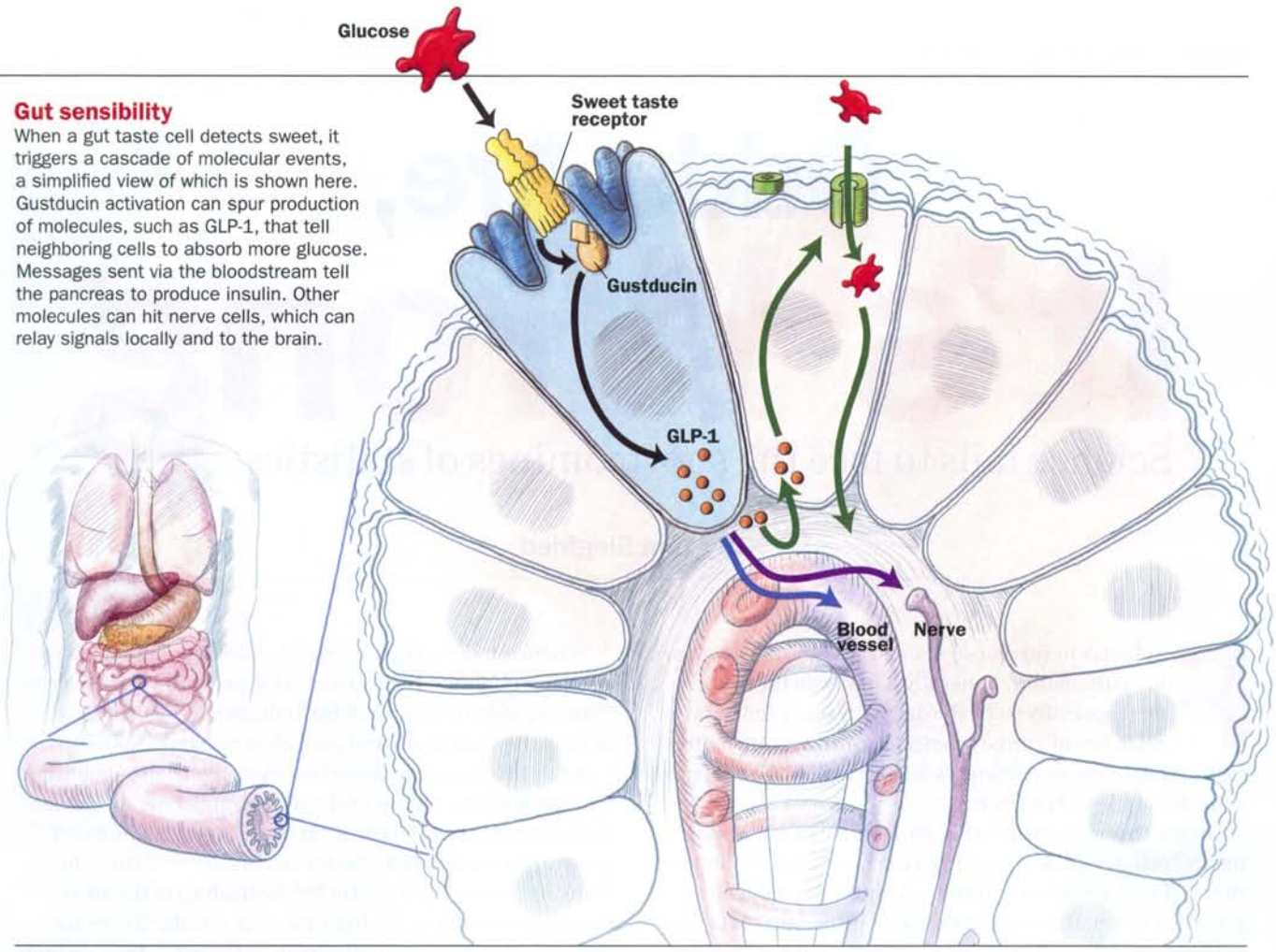
This vast hormonal landscape is a complex one involving multiple signals that might be received locally or far away. Stimulating gut taste receptors leads down roads much more long and winding than those that bring taste from the tongue to the brain, says Jayaram Chandrashekar of the Howard Hughes Medical Institute's Janelia Farm Research Campus in Ashburn, Va. (Chandrashekar is lead author of a recent paper in *Nature* that confirmed the identity of the tongue's salt taste receptor.) When a taste receptor is hit in the mouth, the brain gets the message almost instantaneously. But the effects of triggering gut taste cells may take minutes. "The link between activation and nutrient absorption has to take into account this delay," Chandrashekar says. "It is probably more complicated than the tongue and involves multiple pathways."

This complexity makes gut tasting hard to study, as does the fact that what tastes sweet or bitter to a person doesn't necessarily taste that way to mice and rats, which are often used in lab experi-

Inner taste Activity in taste-related genes and proteins has been found throughout the body, not just in the mouth. For humans, the tongue and cheeks are the usual suspects, but activity has also been identified in the liver, lungs and gut. Mouse taste-related genes and proteins are active in the nasal cavity, brain and even the testes. And fruit flies show activity on the legs and wings, as well as the ovipositor, perhaps so female flies can identify nutrient-rich locations to lay eggs.



● Areas where genes or proteins involved in taste have been found



Gut sensibility
When a gut taste cell detects sweet, it triggers a cascade of molecular events, a simplified view of which is shown here. Gustducin activation can spur production of molecules, such as GLP-1, that tell neighboring cells to absorb more glucose. Messages sent via the bloodstream tell the pancreas to produce insulin. Other molecules can hit nerve cells, which can relay signals locally and to the brain.

ments. For example, sweet taste cells on the human tongue appear broadly tuned to recognize a number of compounds, including the sugars fructose, glucose and sucrose; several artificial sweeteners, such as saccharin (Sweet'N Low) and aspartame; and some amino acids and sweet proteins. But mice, for example, don't seem to respond to aspartame, the sweet of Equal and NutraSweet.

Taste preferences also differ in animals that are more closely related than mice and men, so results may depend on the model organism. Research suggests chimpanzees and gorillas taste aspartame as sweet, while New World primates, such as marmosets and capuchins, don't. (Fruit flies do, scientists reported in 2008.) A recent survey of the sweet tastes of animals in the order Carnivora, which includes lions, house cats, ferrets and dogs, found all of the animals were indifferent to six artificial sugars, except the red (a.k.a. "lesser") panda. The red panda gulped down solutions with aspartame, neotame and sucralose, researchers reported in April 2009 in the *Journal of Heredity*.

Red pandas aren't the only ones that fancy artificial sweeteners. Humans, like their chimp relatives, taste these compounds as sweet. Data from the National Health and Nutrition Examination Survey, conducted by the U.S. Centers for Disease Control and Prevention, suggest that regular consumers of diet drinks slurp more than three 8-ounce servings per day. But if the artificial sweeteners in these drinks are stimulating gut taste receptors, there may be consequences. Three recent studies assessing large data sets found an association between drinking diet soda and the risk of developing metabolic syndrome and type 2 diabetes.

"The diet soda association was not hypothesized and deserves further study," notes one report, published in *Circulation* in 2008. These studies can't establish causation. Indeed, heavier people more at risk of developing metabolic problems may drink more diet soda to begin with. But the results are interesting, notes a commentary published in December in the *Journal of the American Medical Association*. Diet drinks are often enjoyed without food, which means the gut may be preparing for fuel that never arrives.

So beware those little white lies. Thousands of years of evolution have yielded a finely tuned digestive machine, one that recognizes incoming energy and knows how to make the most of it. These intricate chains of events evolved during a time when that sweet zing reliably indicated food rich in valuable calories. And for thousands of years, the gut reacted appropriately.

Perhaps that adage "trust your gut" should be accompanied with another edict: "Tell it no lies." ■

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