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The Science of Appetite

By Jeffrey Kluger

Somewhere in your brain, there's a cupcake circuit. How it works is not entirely clear, and you couldn't see it even if you knew where to look. But it's there all the same — and it's a powerful thing. You didn't pop out of the womb prewired for cupcakes, but long ago, early in your babyhood, you got your first taste of one, and instantly a series of sensory, metabolic and neurochemical fireworks went off.

The mesolimbic region in the center of your brain— the area that processes pleasure — lit up. The vagus nerve flashed signals to the stomach, which began to secrete digestive acids. The pancreas began churning out insulin. The liver cranked up to refine the body's chemistry to accommodate the sugar and fat and starch that were coming in. As all those complex processes were unfolding, your midbrain filed away a simple, primal, unconscious idea: *Cupcakes are good*. A lifetime love affair — perhaps pleasant, perhaps tortured — began.

Human beings have always had a complicated relationship with food. Staying alive from day to day requires our bodies to keep a lot of systems running just so, but most of them — circulatory, respiratory, neurological, endocrine — operate automatically. Eating is different. Like sex, it's a voluntary thing. And like sex, it's a sine qua non to keep the species going. So nature cleverly rigs the game, making sure we pursue them both by making sure we can't resist them. In the case of food, that has lately spelled trouble. Human history has usually been characterized by too little to eat rather than too much. Nature never planned for what could happen when unchecked appetites were suddenly matched by unchecked resources. But we're seeing it now.

Postindustrial humans — as any trip to an all-you-can-eat buffet will tell you — have become a soft, sedentary, overfed lot. It's not just that 67% of the U.S. population is either overweight or obese (including about 17% of children ages 6 to 19); it's that we know that fact full well and seem helpless to control ourselves. We lose weight and routinely regain it; we vow to eat healthfully and almost always lapse. Our doctors warn us about our rising blood pressure and creeping cholesterol, and we get briefly spooked — until we're offered the next helping of cheesecake or curly fries, our appetite shouts down our reason and before we know it, we're at it again. By some estimates, Americans are collectively more than 5 billion lbs. overweight. While in a population of 300 million people that's a more or less manageable 17 lbs. apiece, the weight is not distributed equally. Those of us who are overweight are often grievously so. But all of us pay the cost. "That weight is a shared burden," says geneticist and microbiologist Ronald Evans of the Salk Institute

for Biological Studies in La Jolla, Calif. "Whether it's you or not, it gets factored into the medical health bill."

Just why is our appetite so powerful a driver of our behavior, and, more important, how can we bring it to heel? If that question has long defied easy answers, it's no wonder. Understanding a single biological unit — the heart, the lungs — is hard enough. Understanding a process as complex as appetite— one that involves taste, smell, sight, texture, brain chemistry, gut chemistry, metabolism and, most confounding of all, psychology — is exponentially harder. But science is trying.

Researchers in labs and institutes around the world are peering into the brain to understand the regions where appetite is perceived and satisfied, and pinpointing the receptors on cell surfaces that keep us hungry or get us sated. They're studying the neural wiring of the stomach and intestines, as well as the operation of the genes that drive our appetite, to track how satiety signals are sent and determine why they sometimes get lost. And they're peering back into human history to understand better how we were booby-trapped for overeating from the start and how we might be able, so many eons later, to cut the trip wire at last. "The scourge of body-weight dysregulation has become a leading cause of death worldwide," says Dr. David Cummings, an associate professor of medicine at the University of Washington. "Understanding it is perhaps the most compelling agenda in the field of medical research."

PRIMORDIAL GLUTTONY

If you're among the 200 million Americans who have ballooned past their target weight, you can take some consolation from the fact that your early ancestors would be very proud of you. Human beings emerged into a world in which food often was scarce, often spoiled and— when we learned the art of hunting— sometimes bit back, making the idea of eating a lot when you could both sensible and necessary. If you never knew when you were going to have dinner again, it was best to gorge when the food was there.

"We were hardwired to eat and eat— and particularly eat fatty foods because we didn't get them often," says Sharman Apt Russell, author of *Hunger: An Unnatural History*. We're programmed not only to overeat but also to fail to recognize immediately just when we've reached that point. Mothers tell kids not to wolf their food because it's harder to enjoy it that way and also because even after you've had enough, it can take a while for your brain to get the message. By the time it does, you're not just full; you're stuffed. "The people who didn't immediately lose their appetites, who could gorge themselves and keep going, those people would survive longer during the next famine," says Dr. Jeffrey Flier, obesity scientist and professor at Harvard Medical School.

That's not to say that your body doesn't work hard to keep itself balanced. Over the course of a year, the average adult male consumes about 900,000 calories, yet his weight may not rise or fall by more than a pound. Since a pound equals about 4,000 calories, that means his annual intake is just 0.4%— or 11 calories a day— above or below precisely what he needs to keep going. "You are

within a potato chip a day of matching your intake with expenditure," says Randy Seeley, professor of psychiatry and associate director of the Obesity Research Center at the University of Cincinnati.

It takes a lot to maintain such a precisely balanced cycle of fueling and burning, and in most cases, it all starts with the clock. Like other animals, we are creatures of dietary habit. Feed us at 8 a.m., 1 p.m. and 7 p.m., and we learn to get hungry as those hours approach. Throw in a snack at 3:30 or before bedtime, and we get the itch then too. At all these moments, what's fueling the feeling is a substance called ghrelin.

THE HUNGER HORMONE

Identified in 1999, ghrelin is often called the hunger hormone because that precisely captures what it does. Ghrelin is produced in the gut in response to meal schedules— and, according to some theories, the mere sight or smell of food— and is designed to give rise to the empty feeling we recognize as wanting to eat. When ghrelin hits the brain, it heads straight for three areas: the hindbrain, which controls the body's automatic, unconscious processes; the hypothalamus, which governs metabolism; and the mesolimbic reward center in the midbrain, where feelings of pleasure and satisfaction are processed. That's a neural triple play that guarantees that when ghrelin talks, the brain will listen.

Cummings has conducted studies in which he measured the hormone in people's blood every 20 minutes and found that levels reliably spike as mealtimes approach. Add or subtract a daily meal, and you soon gain or lose a surge.

"Grazing animals have little spikes of ghrelin all day long— 20 to 30 in the case of a rat," Cummings says. One of the reasons gastric-bypass surgery can work in severely obese people — apart from the fact that it reduces the carrying capacity of the stomach— is that it also appears to turn down the ghrelin spigot. An Italian study even looked at ghrelin in anorexics and found that levels of the hormone were chronically high— a chemical alarm that the self-starvers trained themselves to ignore. All this research confirmed ghrelin's role in driving appetite, both when we really need to eat and when we merely expect to.

If ghrelin were all there was to it, we and the rats would eat ourselves to death. But even as one system is gunning our hunger higher, another is standing by to slow things down. The first step in that appetite-taming process occurs in the stomach and upper intestine, where nerves that sense stretching and distension eventually alert the brain that we're getting full. That message is reinforced by three substances that travel northward from the gut. The first, a peptide released by the upper intestine called cholecystokinin (CCK), is the most fleeting of the three, reaching the brain and increasing the feeling of heavy satisfaction that prods you to push away from the table. But CCK does not last long, certainly not long enough to prevent you from eating again well before your body needs more fuel.

Racing in after CCK are two hormones, GLP-1 and PYY, that really slam on the brakes. Produced in the lower gut, they not only tell your brain you've had enough but also tell your stomach to stop what it's doing and not move anything further along into the intestines— where the real business of digestion takes place— until what's there has been broken down some. If you've ever finished a heavy meal at 8:30 p.m. and realized that you still feel stuffed when you climb into bed at 11, that's why. What's more, GLP-1 adjusts blood chemistry, stimulating the pancreas to release more insulin, which soaks up sugars released into the blood by the inrushing food and stores them in the body's fat deposits. "These two hormones go beyond meal intake and regulate overall energy balance," says Hans-Rudolf Berthoud, head of the neurobiology and nutrition laboratory at the Pennington Biomedical Research Center in Baton Rouge, La.

If despite all those obstacles in the path of overeating you still pack in too much food— and as a result pack on too much fat— the body has one other, much bigger gun it can roll out: leptin. An appetite-suppressing hormone discovered in 1994, leptin is produced by body fat itself, usually in direct proportion to how much of the tissue you're carrying. The fatter you are, the more leptin you produce. Once in the bloodstream, the hormone travels to the hypothalamus, one of the same brain regions targeted by ghrelin, seeks out a pair of neuropeptides known to stimulate appetite and partly muffles their signals. The result is, or should be, that fatter people want to eat less. Not surprisingly, the discovery of leptin was huge news in the diet community. Maybe obese people were simply suffering from a shortage of leptin; supplement the hormone with periodic injections, and the fat would dissolve away.

As it turned out, things weren't so easy. For one thing, there are hundreds of millions of obese people in the world, but even after 13 years of study, researchers have found only a handful— on the order of 10 to 20— with a congenital deficit in leptin production or function. In fact, the leptin system in most overweight people works precisely the way it's supposed to, with hormone levels climbing more or less in lockstep with weight. The problem is, at some point the stuff simply stops working— or at least stops keeping pace with the numbers on the scale. When the few people born with a leptin deficit are given supplemental injections, they respond to the treatment. But in other obese people—whose systems have been overexposed to the hormone over the years and thus grown resistant to it—the treatments do no good at all. (Some studies show that leptin sensitivity can be improved by dieting and losing body fat, making supplements a little bit more effective.)

REJIGGERING THE SYSTEM

If we haven't yet figured out how to tame our need to eat, one reason may be that ghrelin, leptin and the handful of other gut chemicals are only the big dogs of the appetite-control system. Researchers have discovered at least two dozen other hormones and peptides that play a role too. Adjusting the levels of just the few we know best is a little like upgrading the quality of the gas in your car and thinking that it is going to boost it from 20 m.p.g. to 75 m.p.g. You may notice some improvement, but if you really want a better, more efficient machine, you have to open the hood

and retool things in a much more fundamental way. That kind of advanced work on the human metabolic engine is just what the new generation of appetite researchers is trying to do.

Carrie Haskell-Luevano, for example, an associate professor of medicinal chemistry at the University of Florida, is peering deeper into the brain, studying the receptor sites on individual neurons to which appetite-control chemicals bond. The receptor array is massively complex, with at least 40 sites known to play a role in carrying feelings of hunger or satiation and 30 more that probably do. Not all of them are created equal, however, and one of the most intriguing is what's known as the melanocortin-4 (MC-4) receptor.

MC-4 is the neural gateway for ghrelin, leptin and up to 20 other chemicals. Haskell-Luevano and other scientists have found at least 11 genetic mutations in some obese people that appear to cause the MC-4 receptor to malfunction. In some cases, the receptor may fold improperly on the surface of the cell; in others, chemicals may bond imprecisely to it. Either way, appetite regulation can get scrambled but good. "Basically," says Haskell-Luevano, "if you block the MC-4 pathway, hormones like leptin don't work."

Haskell-Luevano is also looking at the adjacent MC-3 receptor, which, while not as powerful as MC-4, does help the brain govern energy balance and can have mutations of its own. Still, genetic problems in these two receptors would not explain all cases of obesity or even very many. Only about 6% of adults and children considered obese have any MC-4 anomalies, though Haskell-Luevano suspects that other irregularities in the genetics of metabolism or appetite control could push the overall total of gene-based obesity closer to 25%.

Flier, of Harvard, is studying neurons in the hypothalamus that are supposed to produce a protein that responds to leptin but, for as-yet-unclear reasons, sometimes fail to. Find ways to stimulate those neurons— or even add doses of the protein they're failing to make— and you could theoretically restore appetite balance. And Evans, of the Salk Institute, is studying cellular receptors known as PPARs, which control the flow of sugar and fat throughout the body. After a meal, fatty acids enter cells, triggering the receptors to rev up the body's energy-burning motor. The more active this system is, the more fat you'll burn; what you don't use gets stored. If you're obese, there's a good chance your PPAR system is idling too low.

"We'd like to use a drug to boost metabolism so you're more efficient at burning," says Evans. Working with mice, he has conducted precisely those kinds of studies, developing drugs that stimulate PPARs and boost fat burning. Five pharmaceutical companies are conducting similar studies, at least two of which have now moved onto human subjects.

Another, entirely different avenue of research is being pursued by Michael Cowley, neuroscientist and associate professor of physiology and pharmacology at the Oregon National Primate Research Center. Cowley is interested in how excessive eating mirrors the patterns of drug addiction. Few people who compulsively consume— whether the substance of choice is food, drugs, tobacco or alcohol— are unaware that their habit could kill them. Yet few have the power to stop, at least not

easily. "The phrase comfort food hits the nail on the head," Cowley says. In the case of both food and drugs, ghrelin again appears to play a role.

While the hormone affects three areas of the brain, it hits the mesolimbic reward region particularly powerfully. Studies of this part of obese people's brains reveal a level of activity remarkably similar to that in the brains of drug addicts when they are exposed to their preferred substance. What's more, in both kinds of people, there is a general deficit of activity in the mesolimbic region, which suggests that the compulsive intake of food or chemicals may simply be an attempt to compensate for this shortfall. Cowley has a financial stake in this argument, since he is the founder and chief scientist of a pharmaceutical company that has now moved to human trials of an antiobesity drug designed to calm the cravings in the reward pathway.

WHAT CAN YOU DO?

Breakthrough drugs are hard to plan for, and if you're trying to get your appetite under control today, they do you no good at all. But other studies in the appetite field could produce results sooner. At the Pennington Center in Baton Rouge, investigators run what may be the most sophisticated metabolic test kitchen in the country, hoping, in part, to determine which kinds of meals satisfy us best with the smallest penalty to pay on the scale. The kitchen looks like any other, with the exception of the laboratory instruments that allow investigators to determine the metabolic impact of eating, say, 90 grams of a pancake breakfast as opposed to 113 or 123. People battling weight problems volunteer for several-day stays to test the menus and undergo other studies in order to help both themselves and others.

At the moment, some of the research in the kitchen involves trying to find a more precise way to balance the glucose loads various foods deliver to the body. That's important, since the bigger the glucose hit, the greater the sense of satiation, but only for a little while. Afterward, hunger returns stronger than ever. "High glycemic foods like refined breads and sugars push the body to refuel," says nutrition scientist Marlene Most, head of the metabolic kitchen. "In low glycemic foods, there is a constant flow of glucose and insulin, so we don't need to refuel as much."

Pennington neuroscientist Christopher Morrison has looked at another, comparatively fast-track approach to appetite control. If leptin supplements have been such a disappointment in keeping food intake in check, what about leptin combined with other natural suppressants such as CCK? In animal studies conducted in a lab where Morrison did his postdoctoral work, doses of CCK followed by leptin did a better job of curbing appetite than either one alone. "There have been some good data to suggest that the [effectiveness] of short-term CCK signals are influenced by the presence of leptin," Morrison says.

Other, still more direct strategies rely on other, still simpler mechanisms. Most people on diets notice that their hunger pangs seem to diminish over time. Perhaps they're just getting used to living with their cravings, but the recent findings showing that leptin may become more effective

as obese people shed fat suggests a biochemical mechanism is at work. While knowing this won't make the weight fall off faster, it does provide one more incentive to stay the dietary course.

Barbara Rolls, a professor of nutritional sciences at Pennsylvania State University, advocates another way to attack hunger even more aggressively. Rolls currently tops the best-seller lists with a book about what she calls the "volumetrics" eating plan— the kind of prefab word that cries out diet fad but in this case describes a sensible idea, provided that it's followed in moderation. The key to volumetrics, Rolls explains, is to consume foods that are high in volume but not in calories in order to stimulate the digestive system's distension nerves. It's the difference between, say, a large, filling salad with a low-calorie load and a small, unfilling brownie with a high one.

"This whole idea of eating smaller portions—I'm really fed up with it," Rolls says. "It's not big portions that make you eat more. It's big portions of calories. If you eat big portions of fruits and vegetables, they displace other foods." Rolls stresses that it's important to eat a variety of tastes and textures. If you overload on one thing— say, the heavy dose of meats that the low-carbohydrate Atkins plan recommends— you're going to crave the sweet or crunchy or doughy experience of the fruits and breads you're forbidden. "It's called sensory-specific satiety," she says, and it's one of the reasons we still have the appetite for a sweet dessert even after we stuff ourselves with a heavy dinner.

The very discordance between a mouthful term like *sensory-specific satiety* and the uncomplicated joy of a crème brûlée at the end of a meal speaks to the puzzle that is the human appetite. We may always be pleasure-seeking creatures, intoxicated by the very experience of food— with its colors and textures and notes of flavor— but that doesn't mean our ancient impulse to eat whenever we can must always yield to our modern ability to satisfy that urge. The same human brain that invented the food court and the supermarket must now develop ways to control how we use them. Just as when we were learning to eat on the savanna, our health and even survival may be at stake.

—Reported by Dan Cray/Los Angeles, Elisabeth Salemme/New York and Carolyn Sayre/Baton Rouge

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