New Hope in the Search for a Treatment for Obesity

A study finds that the medication setmelanotide led to dramatic weight loss in two teenagers with an obesity disorder

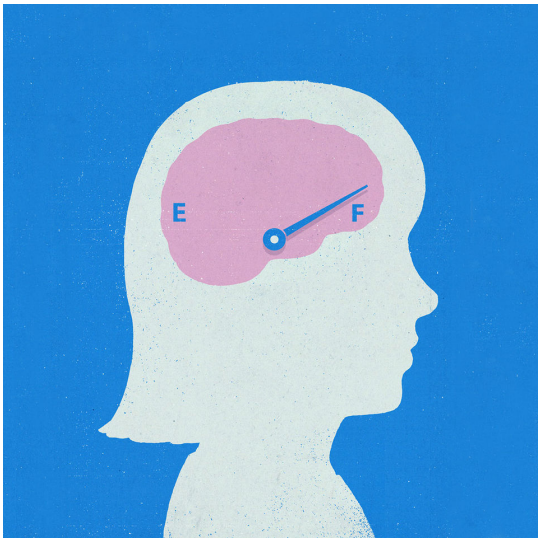

ILLUSTRATION: DAN PAGE

By **MELVIN KONNER**
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Obesity is a massive health threat across the globe and remains hard to counter, despite many thousands of diets and medications. A study published in July in the New England Journal of Medicine gives a few severely obese patients a new medical ally—and the world a narrow ray of hope. Though the study focused on just two patients, their conditions were severe, and the success of their treatment was dramatic.

As infants, the two unrelated girls were on the extreme high end of the normal weight range for 1-year-olds, but by the time they reached 17, they were almost triple the average weight for their age. They started the treatment at age 17 and 18, when they weighed, respectively, 336 and 341 pounds. The new treatment's impact: a weight loss of 33% in 42 weeks for one and of more than 13% in 12 weeks for the other. Peter Kühnen of the Charité hospital in Berlin, the lead author of the study, said in an interview that during ongoing treatment for months after the initial period, the subjects have continued to lose weight without problematic side effects.

The treatment addresses a rare genetic problem. "If you think of yourself at the hungriest moment of your life, that's how these patients feel every minute of every day," said Dr. Keith Gottesdiener, a co-author on Dr. Kühnen's report and chief executive of Boston-based Rhythm Pharmaceuticals, which makes setmelanotide, the medication used in the study.

In the body, one path to satiety—the feeling that we are full—starts when fat cells produce the hormone leptin. In turn, leptin stimulates a gene to make the substance pro-opiomelanocortin or POMC ("pom-see"). POMC is spliced into key hormones, one of which moves through the brain to reach receptors on brain cells that send the message, "I'm full."

In the girls and others being studied, the POMC-producing gene is defective. This malfunction thwarts the chain of messages that normally lead from the stomach to the brain. But when a patient takes setmelanotide, it stimulates the brain's melanocortin-4 receptor directly and ends hunger. (Molecules smaller than setmelanotide—it's of a middling size—have caused worrisome side effects when used as medications, but so far setmelanotide hasn't had this problem.)

Dr. Kühnen estimates that only a few hundred people have this particular genetic disorder and says that they have "absolutely no other option." Last January, the U.S. Food and Drug Administration gave setmelanotide approval in the categories of both "orphan drug" and "breakthrough therapy," meaning that the drug works for a rare disease and can be fast-tracked for scientists and patients.

The two girls in the New England Journal of Medicine report had an 80% reduction in their hunger score, a ranking of hunger pangs. Dr. Gottesdiener notes that setmelanotide brings an added benefit—not only does it decrease appetite, but it increases a patient's energy output.

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The researchers are pressing ahead with more studies on POMC-deficient patients and others with related mutations. Interestingly, Labrador dogs, as a breed, often have a POMC defect and become obese; the drug may help them as well. Beyond these genetic problems, the scientists are extremely cautious about generalizing, aware of false hopes raised by obesity treatments in the past.

Just two girls for now, but the treatment made a huge impact on their lives

Toward the end of their report, the authors write, "We speculate that setmelanotide may also be effective in nongenetic forms of obesity." If that were the case, the drug might work against two major problems of obesity: patients with "leptin resistance," in which the brain doesn't respond to the presence of the hormone, and weight rebound after dieting.

Though the researchers remain cautious and wider obesity trials are some time away, the rest of us can hope that, unlike past treatments, this one may someday help not hundreds but millions.