

# Leptin's Legacy

BY DAVID TENENBAUM ■ ILLUSTRATION BY BRIAN STAUFFER

WHEN JEFFREY M. FRIEDMAN, an HHMI investigator at The Rockefeller University, announced in 1995 that he and his colleagues had discovered a hormone called leptin that melted away fat in obese mice, the *New York Times* wrote, “researchers have found what they hope will be a magic bullet for obesity, or at least the forerunner of major new therapies.”

Scientists, of course, approach any notion of a magic bullet with supreme skepticism, if not total disdain. But electrified by leptin’s potential for the treatment of obesity—the mice had lost 30 percent of their body weight in just two weeks—business pounced on the discovery. With more than half of U.S. adults overweight or obese, a cure would be a major advance in public health. Moreover, the treatment was sure to be a cash cow for its marketers. The biotech company Amgen paid \$20 million to license the hormone.

When Amgen sponsored a large clinical trial of leptin, however, few participants lost weight, dashing hopes that the hormone could curb obesity. “Treatment with high-dose leptin did not achieve the clinical or commercial hurdles necessary,” says Amgen spokesperson Christine Brown. “The company is not looking further at using leptin in normal adult obesity.”

That first look at leptin might have stopped everything, but scientists kept digging. They had compelling reasons to persist, such as Friedman’s dramatic finding that leptin also lowered resistance to insulin in those obese mice.

Today, studying leptin’s role in metabolism while continuing to explore its therapeutic possibilities, Friedman and others are beginning to piece together the mechanisms through which the hormone affects several systems in the body. And, importantly, leptin has been found to treat successfully—possibly even cure—two rare diseases: a defect in the leptin gene and lipodystrophy, a disease caused by the absence of fat cells, which the body relies on to make leptin.

## ADJUSTING THEIR SIGHTS

Stephen O’Rahilly, an endocrinologist at the University of Cambridge, has given leptin supplements to extremely obese children who have a defective leptin gene. The children, he says, “are constantly hungry, are eating frozen food without thawing it. Their lives are dominated by the search for

Once touted as a possible cure for obesity, the hormone leptin couldn’t trim America’s waistline, but it has led to a focus on the biology of obesity—and to treatments for two rare diseases.

food.” Treatment with leptin, he adds, is “utterly dramatic. With a once-a-day injection, you are essentially taking almost wheelchair-bound children and changing them into near-normal children.” Elif Oral (now at the University of Michigan) and her colleagues at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) achieved similarly remarkable results by using leptin to treat lipodystrophy (see sidebar, page 26).

Perhaps equally important may be leptin’s impact on insulin for some people with type 2 diabetes. “It’s very clear in a number of settings that leptin can improve diabetes,” Friedman remarks. “Its usefulness is not limited to lipodystrophy patients.”

Thus, even though leptin did not live up to initial expectations that it would cure obesity, it has since proved to be an invaluable research and therapeutic tool. Peter J. Havel, a nutrition researcher at the University of California, Davis, says that by “demonstrating that body weight is a physiological parameter regulated by hormones, leptin opened up the whole field of obesity research.” Leptin experiments, O’Rahilly adds, have debunked the notion that obesity results from people’s “immorality, behavior and gluttony.”

## RESISTANCE VERSUS DEFICIENCY

The leptin story began in 1950, when researchers at The Jackson Laboratory in Bar Harbor, Maine, noticed that they had a strain of mice that were obese, lethargic, insulin-resistant and constantly hungry. This so-called *ob/ob* mouse, Friedman says, “lives in a state of perceived starvation, so ironically it becomes fat.” The scientific explanation finally emerged in 1994, when Friedman and his colleagues found the mutated *ob* gene responsible for the syndrome. The next year, they purified the normal *ob* gene’s product, a hormone they dubbed leptin for the Greek word *leptós*, which

means “thin.” When they gave the obese mice leptin supplements, the animals lost weight, became more active and began responding to insulin.

At first, leptin seemed to be simply a signal sent by fat cells to the brain: “We’re full. Stop eating.” But as leptin research took off—the hormone has been the subject of more than 4,200 scientific papers since 1995—the picture became more complicated. Scientists found large numbers of leptin receptors on the hypothalamus, a brain structure known to control appetite. Many other effects of leptin—or the absence of leptin—seem to work through the blood, Friedman explains, adding that the hormone “modulates T cells, macrophages, platelets and a whole host of other physiological systems” (see diagram).

In retrospect, it seems clear why so many people in the Amgen clinical trial failed to lose weight, says Friedman. Obese people have many fat

cells, and they generally make lots of leptin. Therefore, obesity results more often from a failure to respond to leptin than from an absence of leptin.

Although most people in the trial may have had sufficient leptin, a subset was probably deficient in the hormone, says Friedman. “Fifteen to 20 percent of the obese people [in the study] did in fact lose significant amounts of weight. A key unresolved issue concerns the plasma level of the hormone below which a robust biologic response can be predicted,” he adds.

“I don’t want to protest too much, but it’s as if we found that the majority of adult-onset diabetics don’t respond to insulin, and concluded that insulin has nothing to do with lowering glucose.” In other words, leptin resistance in the majority of participants may have masked leptin deficiency in the minority. Friedman and his colleagues are now trying to identify obese people who have low concentrations of leptin

## Proof Positive

WHEN CHRISTINA VENA, a girl from Vineland, New Jersey, entered puberty a few years ago, her fat cells atrophied and disappeared. She grew extremely thin and obsessed with food. “I thought I was starving,” she recalls. “My parents had to lock the kitchen cabinets, or I’d eat until I got sick.”

Christina had a rare metabolic disorder called lipodystrophy. She also had type 2 diabetes, and her blood contained more than 50 times the normal concentration of triglycerides, a fat precursor. Lacking fat cells, she stored fat in her liver and in lesions under her skin. These pockets of fat were so painful that Christina could not dress or bathe herself.

Doctors at the National Institutes of Health (NIH) could not treat Christina’s underlying disease, so they cleaned her blood of triglycerides weekly, in a procedure akin to kidney dialysis. “When I first went to NIH, they said there was nothing they could do,” Christina says. “They said I would probably die from it. It was pretty extreme.”

In 1995, about the time her symptoms began to appear, HHMI’s Jeffrey Friedman discovered the hormone leptin. Although people with lipodystrophy are extremely skinny, their insatiable hunger resembles that of the obese mice Friedman studied. When Christina’s doctors at NIH found that her body was making no leptin, they decided to test leptin supplements. “The logic was that if you are deficient in the hormone, and we give you the hormone, you may very well respond,” says Phillip Gorden, then director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

In July 2000, Elif Oral and her colleagues at NIDDK began a study of Christina and eight other girls and women with lipodystrophy. When they gave Christina leptin injections, the results were swift and dramatic. The compulsive eating, the blood cleansing, the horrid skin lesions—even the rude stares of classmates—became memories. “I’m not hungry all the time,” says the 20-year-old sophomore at Rowan University in Glassboro, New Jersey. Her life is consumed by schoolwork and a job, ironically enough, making sandwiches in a deli. Sounding a bit awed by something that most people take for granted, she adds, “I can eat a little bit and be full.”

Christina and the others in the lipodystrophy study also experienced another positive effect seen in Friedman’s original animal experiments: a great reduction in what Gorden calls the “extreme form of insulin-resistant diabetes” that is typical of lipodystrophy. Leptin somehow increases sensitivity to insulin, perhaps by redistributing fat. As a result, most of the people in the lipodystrophy study were able to stop taking medicine to control the high concentrations of sugar in their blood. “I’ve been involved in insulin resistance for 35 years,” says Gorden. “To treat patients with something that has such remarkable benefits was quite gratifying.”

Christina now seems cured, but her body may some day stop responding to leptin. Or it may start making antibodies to leptin. Although resistance has occurred in some people who are receiving leptin supplements, their treatments continue to work, according to Stephen O’Rahilly of the University of Cambridge.

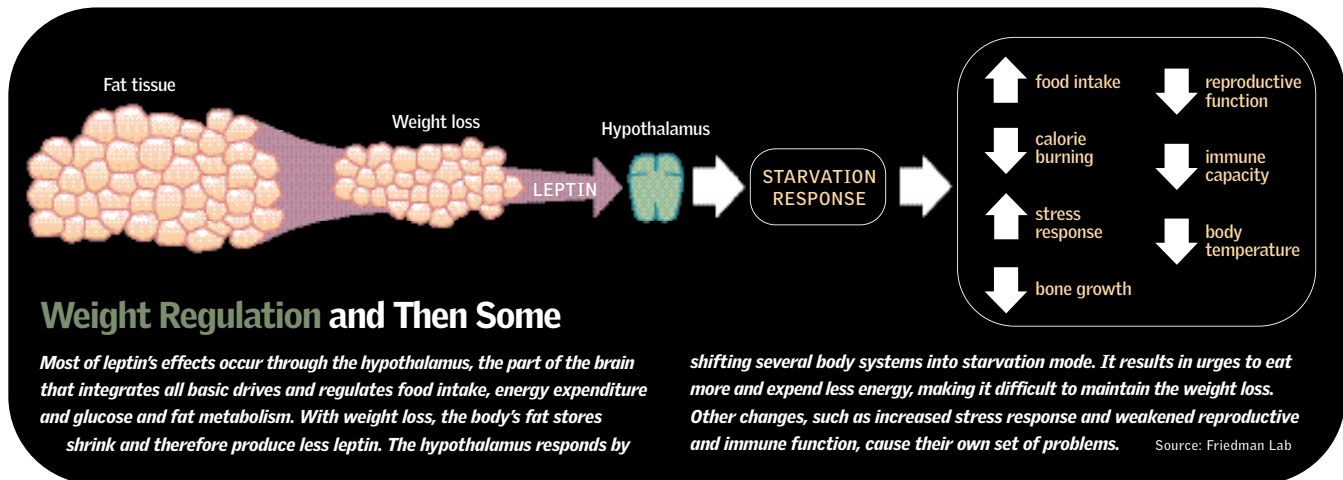
For three years, leptin has allowed Christina to attend college, hold a job and feel like a fairly normal young woman. “I consider myself cured,” she says. “I’m still really skinny, but I don’t have any symptoms that I can’t live with.”

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DAVID GRAHAM

*Christina Vena is back to living a normal life—she’s not incessantly hungry, her diabetes is gone and she’s in college studying special education.*



and might therefore benefit from supplements.

To treat leptin resistance, scientists must have a better understanding of the signaling pathways activated by the hormone. Studies of two components of those pathways were published in 2002.

Friedman and James M. Ntambi, a biochemist at University of Wisconsin–Madison, measured the effect of leptin on the expression of 12,000 genes that seem to be active in the liver. The biggest change occurred in the expression of the gene that makes an enzyme called stearoyl-CoA desaturase-1 (SCD-1). SCD-1 helps determine whether the body stores fat or burns it. When the researchers removed the gene for SCD-1 from their *ob/ob* mice, they discovered that the animals' metabolism returned almost to normal. Even though the mice made no leptin, they were not obese. Moreover, says Ntambi, "these animals are more insulin-sensitive and don't become diabetic." The results help show how leptin works. "For years the mechanism was a black box," says Ntambi. "Now we know that SCD-1 is on one pathway of leptin's actions."

Barbara B. Kahn, an endocrinologist at Harvard Medical School and Beth Israel Deaconess Medical Center in Boston, reported on a different leptin pathway involved in fatty acid metabolism in muscle. Like Ntambi, she says her study shows that pathway research may lead to drugs that improve leptin's efficiency by sidestepping resistance to the hormone and activating molecules further along the signaling pathway.

#### PREVENTING STARVATION

"There are a lot of interesting hypotheses [about leptin] out there," says Phillip Gorden, former director of NIDDK, who now does research there. "Some people think it's a protective mechanism against starvation, some think it's a satiety signal and some think its major role is to control lipid distribution," directing the body to store fat in fat cells rather than in, say, the liver, where fat deposits are linked to disorders such as diabetes.

The many, seemingly unrelated effects of leptin, Friedman says, may have evolved to provide a "link between the nutritional state and the physiology and behavior of an animal," enabling it to adapt to starvation. The fact that one fat-derived molecule affects metabolism,

reproduction and immune status may represent evolutionary efficiency, he adds. "Leptin is designed to measure the amount of fat you carry, and once you have a molecule that can signal that, it's logical that it would send that signal to a number of physiologic systems."

The leptin gene apparently conferred a selective advantage on our ancestors by enabling them to survive lean times. These days, the challenge in developed societies is to remain lean during flush times: Obesity and diabetes are far more threatening than starvation. Indeed, studies emanating from the discovery of leptin emphasize how hard it is to lose weight. Randy J. Seeley, a neuroscientist at the University of Cincinnati who studies appetite regulation in the brain, points to the melanocortins, a group of leptin-sensitive neuropeptides that help regulate energy balance. Although drugs that target the melanocortins might result in lower food intake, he says, the control of food intake is complicated and inclined toward storing, not burning, fats. "You were not built to lose weight, you were built to not starve to death."

Although leptin was not a magic bullet for obesity, many researchers say the discovery of the hormone has changed forever the study of obesity, diabetes and metabolism. "Leptin was so successful in the rodent model that people immediately became excited about it as an obesity treatment factor," says Gorden. "In reality, that was probably an enormous leap of faith."

Still, Gorden adds, leptin's ability to treat—and possibly cure—two rare diseases has renewed hope that it, or a compound discovered through it, may help treat obesity, diabetes and other devastating metabolic disorders. Leptin, he says, "offers a window of opportunity that we didn't have before."

Friedman says the window is wide open, and in the February 7, 2003, issue of *Science*, he called for a large effort aimed at understanding the biology of obesity. Now that a molecular framework of the system that regulates body weight is in hand, he says, it's time to define the genetic differences between lean and obese and figure out how environmental and developmental factors alter the function of this system. Only from this, he says, will come rational therapies to combat obesity and its complications. **H**

Jeffrey Friedman is now looking at genetic factors in obesity.



MARC BRYAN-BROWN