"Obese" Protein Slims Mice

Researchers find that injections of the protein product of the mouse obesity gene cause overweight mice—and normal ones as well—to lose weight

In the United States, losing weight is a national obsession. According to statistics compiled by the National Institutes of Health, up to one third of all Americans are overweight, and they spend more than $30 billion per year in their efforts to trim the fat. More than vanity is at stake: Obesity is the cause of a myriad of serious health problems, from adult-onset diabetes to heart disease. All too often, however, those weight-loss efforts are doomed, as almost everyone who sheds the excess pounds gains them back in 1 to 5 years. Now, new research raises hopes of a solution to this problem.

In this issue, three independent research teams report that the protein product of the mouse *obese* gene (*ob*), identified late last year, when injected into mice, causes the animals to lose weight and maintain their weight loss (see pp. 540, 543, and 546). "I'm really impressed," says Richard Atkinson, an obesity researcher at the University of Wisconsin, Madison. "The level at which body weight is defended is reduced by this stuff." If the protein were to act similarly in humans, it might form the basis for an effective weight-loss drug.

Indeed, just such a possibility led Amgen Inc., a biotech firm in Thousand Oaks, California, to pay an unprecedented $20 million to Rockefeller University in New York City for an exclusive license to develop products based on the *ob* gene (*Science*, 5 May 1995, p. 631). Any dreams of cashing in on a treatment for obesity are far from realized, but they do seem a bit closer to reality with the three reports in this issue. One comes from a team led by Jeffrey Friedman, a Howard Hughes Medical Institute (HHMI) investigator at Rockefeller, whose lab reported the cloning of the *ob* gene in *Nature* last December, and Stephen Burley, also an HHMI investigator at Rockefeller; another is from a team led by Frank Collins at Amgen; and the third comes from Arthur Campfield and his colleagues at Hoffmann-La Roche Inc. in Nutley, New Jersey.

All three groups injected the Ob protein into mice that are grossly obese because they have two mutant copies of the *ob* gene (known as *ob*/*ob* mice). As a result, the mice curbed their eating and shed fat. In Friedman's experiments, for example, *ob*/*ob* mice that weighed 65 grams, about twice the weight of normal mice, had dropped 40% of their body weight after a month of daily injections of the Ob protein.

There were hints that the Ob protein would work like this, from work done in the 1960s and '70s by Douglas Coleman at the Jackson Laboratory in Bar Harbor, Maine, where the *ob* mutation was first discovered in the 1950s. Coleman indirectly connected the circulatory systems of adult *ob*/*ob* mice to those of normal mice, and the *ob*/*ob* mice lost weight. This suggested that their obesity could be corrected by a weight-regulating substance from the blood of the normal mice. The recent experiments not only confirm Coleman's results, but they go further to suggest how the protein produces weight loss.

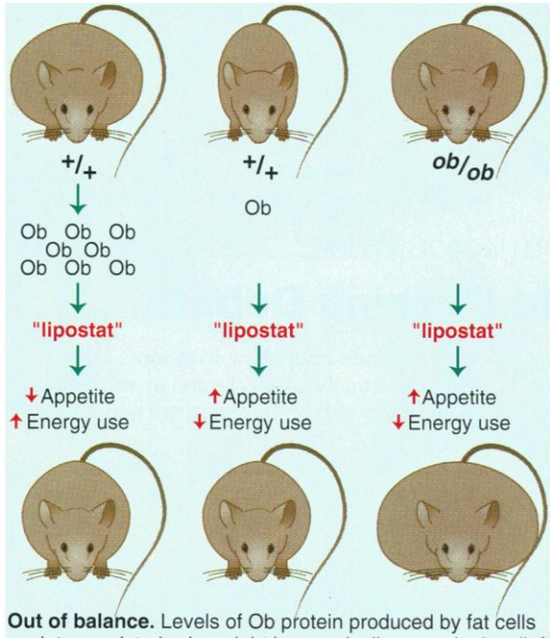


ILLUSTRATION: K. SUTLIFF

Out of balance. Levels of Ob protein produced by fat cells work to regulate body weight in genetically normal mice *(left and middle)*. But in a mutant mouse lacking a functional *ob* gene *(right)*, weight gain goes unchecked.

The present studies indicate that the Ob protein has a dual action: It turns down the animals' appetites and increases their energy use, causing them to burn more fat. Friedman's team measured the daily food intake of *ob*/*ob* mice that were receiving the Ob protein and then fed the same amount to an identical set of untreated *ob*/*ob* mice. Even on the same diets, the mice treated with the Ob protein lost 50% more weight than did the untreated animals, suggesting that food intake alone can't account for the Ob-induced weight loss. Results from the Amgen group provide a possible explanation for the difference. These researchers showed that the protein boosts the animals' energy use in at least two ways: It makes the otherwise sluggish *ob*/*ob* mice more active and also speeds up their slow metabolisms.

But as promising as these results are, they don't necessarily translate to obese humans, because preliminary studies of the human *ob* gene suggest that the common forms of human obesity aren't due to anything as simple as a flaw in the *ob* gene. "Obesity is a polygenetic disease" in humans, says Roche's Campfield. "The evidence suggests that you inherit a genetic predisposition to gain weight on a high-fat diet."

With that in mind, researchers have begun testing the Ob protein using mouse models that more closely resemble the human situation. They are getting some encouraging results. The Roche team is working with a strain of mice which, like many humans, grow plump when their diet contains too much fat, a condition called diet-induced obesity (DIO). After fattening up some of these mice, Campfield and his colleagues injected them with Ob protein. In response, the animals ate less of their high-fat food and lost weight.

Collins of Amgen says his group has similar unpublished findings with a different strain of mice that shows another typically human trait—they stay trim in their youth but put on weight as they get older. As with the DIO mice, these "maturity-onset" obese mice lost weight when they were injected with the Ob protein. "Essentially we're seeing the same result," says Collins: "a kind of obesity that is not caused by mutation of the *ob* gene is correctable by the Ob protein."

Ob also causes weight loss in mice that aren't even obese. All three groups showed that normal mice ate less when injected with the protein, and Friedman's group found that mice receiving a relatively high dose of the protein lost 12% of their body weight and virtually all of their body fat in 4 days, and maintained that new weight for the 2 weeks that they continued to receive injections.

The Ob protein may control body weight through a feedback system that tells the body how much fat it carries. Friedman's group has

shown that the Ob protein is made by fat cells. They propose that some part of the body reads Ob levels the way a thermostat reads temperature and then tells the body to make the appropriate adjustments. If the levels are low, Friedman explains, this "lipostat" tells the body it doesn't have enough fat and needs to gain weight. If they are too high, the message is to eat less, burn more calories, and lose weight.

Mutant *ob/ob* mice make no Ob protein, and so, according to the model, their lipostats go unchecked, and they gain weight. But other obese mice, whose fat cells are making Ob protein, may be fat because their lipostats simply have a higher set point, requiring higher levels of Ob protein before they tell the body to lose weight. Injected doses of Ob protein may act in those mice like "virtual fat," fooling their lipostats into sensing that they are fatter than they are and triggering weight loss.

As a first step toward testing that model, researchers are searching for the target tissues for the Ob protein. At least one target seems to be in the brain; the Roche team reports that Ob protein injected directly into the brains of mice caused effects similar to those produced by injections into the bloodstream, but at a much lower dose. "We see reduced food intake and a loss of body weight," says Paul Burn, director of the Department of Metabolic Diseases at Roche. "That suggests the receptor for the Ob protein is localized in the brain." Many research teams are also hot on the trail of that receptor itself, which transmits the protein's message via a set of as-yet-unknown signals inside cells. Identification of the receptor "may eventually lead to novel drug targets within the signaling cascade," says Burn.

But while that research proceeds, all eyes are on the potential for Ob itself to be developed into a weight-loss drug. While the mouse studies are encouraging, "it is too early to be sure what the clinical implications will be," cautions Ruth Harris, a physiologist who studies obesity at the Pennington Biomedical Research Center of Louisiana State University in Baton Rouge. "A lot more work has to be done [on Ob protein levels in humans] to have a better understanding of the role it plays in obesity," she says.

Friedman readily agrees that much work must be done before considering the use of Ob in humans. "There is an orderly series of steps ... and that process has to be followed carefully," he says. "The next important step is to establish the safety of the protein in animals." Even if the early promise holds up, there is the matter of drug delivery. Because Ob is a protein, it can't be taken in pill form, as it would be destroyed in the digestive tract, and so would have to be injected, perhaps daily. But "for someone who is morbidly obese, it wouldn't be a problem for them to take an injection," says Larry Bellinger, a physiologist who studies obesity at Baylor College of Dentistry in Dallas.

If the Ob protein were to lead to a weight-loss drug, that would raise thorny questions about how such a drug should be used. If the mouse studies are an indicator, the drug might enable normal-weight people to become super-thin or allow fat people to drop pounds without changing their high-fat diets, which carry their own health risks. "That is a little scary because it could be abused," says Atkinson. "Maybe ... everyone will want to look like Twiggy."

Anyone concerned with how such a drug might be used or misused will have plenty of time to mull the issue over while researchers follow up these early results—and Amgen waits anxiously to see whether its $20 million investment will pay off.

–Marcia Barinaga

PALEOANTHROPOLOGY

New Foot Steps Into Walking Debate

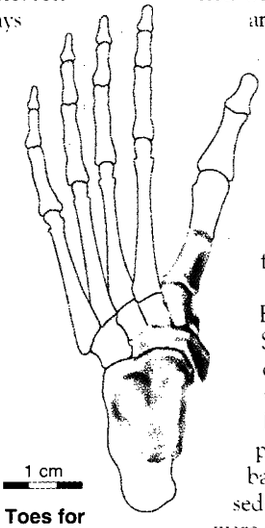
There's no doubt that our early ancestors walked on two legs—footprints left in the ground in Tanzania some 3 million years ago leave a firm record of their evolutionary strides. But anthropologists are in sharp disagreement over how much walking these creatures actually did. Did they spend their time wandering open savannas, or clambering up and down tree trunks in more wooded places? Because modern humans are fully grounded, and the apes we came from are not, researchers dearly want to know when the shift occurred.

With a report on the left foot of an early human forerunner, or hominid, that they've dubbed "Little Foot," anthropologists Ronald Clarke and Phillip Tobias of the University of the Witwatersrand Medical School in South Africa step into this debate—and onto the toes of some of their colleagues. On page 521 of this issue, the two researchers describe four bones they've found—probably from a hominid called an australopithecine that lived about 3.5 million years ago—that make up an arch running from the heel of the foot down to the beginning of the great toe. They are the first connected foot bones ever found from a single such creature.

And while the foot shows some humanlike traits, such as a weight-bearing heel obviously adapted to bipedalism, Tobias says its long, flexible big toe is perfect for grabbing onto tree limbs and, along with some other traits, it "virtually settles the argument" that our ancestors at that time were still partly in the trees.

"I find it conceptually and theoretically a very compelling paper," says Randall Susman of the State University of New York, Stony Brook, long an advocate of arboreal ancestors. "The back part of the foot around the ankle joint is very human, but as you get out toward the toes, they get more and more apelike." Elwyn Simons of Duke University in North Carolina, who recently viewed the bones, says that "it's very important because all the other foot bones [found up to now] didn't really show as clearly the climbing ability."

Critics, however, react to Little Foot as if they've been kicked. "Their conclusion is patently absurd," says Owen Lovejoy of Kent State University in Ohio, a champion of early unabridged bipedality. The australopithecine hip, knee, and spine have been adapted for an upright life, he says, and to ignore all that evidence in favor of one foot joint "is mechanically and developmentally naive."



Toes for climbing? Foot bones from a human forerunner.

Anthropologists such as Susman and Lovejoy have been "butting feet"—as one onlooker calls it—over this issue for more than a decade. Susman's camp, for instance, has argued that curved fingers and toes from *Australopithecus afarensis* (the species identified with the famous "Lucy" skeleton) are "arboreal hooks" much like those seen in modern apes. Lovejoy and several colleagues have countered that the pelvis and other anatomical traits show that such early hominids were already grounded, and that any apelike traits they still carried were unused baggage from their evolutionary past.

Into this debate now steps Little Foot—more properly known as Stw 573 for the Sterkfontein cave in South Africa in which it was found. The creature was at least 3 million years old, and probably as much as 3.5 million, based on geologic dating of the sediments in the cave. The bones were originally excavated in 1980, but it wasn't until last year that Clarke put all the pieces together. He found an ankle bone (talus), some foot bones, and the first part of a big toe. "All jointed perfectly together when you held them one against the other," Tobias recalls.

One of these joints in particular—the