Mouse Obesity Cured by Hormone

Forty-five years ago, a spontaneous mutation in a then-unknown mouse gene caused some extraordinarily obese mice to appear in the breeding colonies of Jackson Laboratory in Bar Harbor, Maine. Researchers have now shown that injections of the hormone produced by this gene in its unmutated form cause the obese descendants of those mice to shed weight dramatically.

Perhaps more important, in terms of developing treatments for human obesity, similar injections also produced weight loss in normal mice and in mice whose obesity stems not from a genetic flaw but from a high-fat diet.

The framework of this mouse weight-loss plan formed last year when a research group led by Jeffrey M. Friedman of the Howard Hughes Medical Institute (HHMI) at Rockefeller University in New York City finally isolated the gene, *obese*, responsible for Jackson Laboratory's overweight strain of mice (SN: 12/3/94, p.372).

Friedman and his colleagues established that the gene is turned on in fat cells, where it directs the synthesis of a hormone—a protein that is secreted by cells and that circulates in the blood. The team suggested that this hormone, which it named leptin after the Greek word for thin, directly or indirectly tells the brain how much fat an animal has stored. This feedback would then regulate a mouse's body weight by affecting its eating behavior.

At the time, Friedman and others speculated that the obese mice failed to make leptin because of their defective gene and that administering the hormone would suppress appetite and produce weight loss. But, says Friedman, "it's one thing to speculate, it's another thing to show it."

Three independent research groups—one led by Friedman and fellow HHMI investigator Stephen K. Burley, also at Rockefeller; a second headed by Frank Collins of Amgen, a biotech firm in Thousand Oaks, Calif.; and the third including L. Arthur Campfield and Paul Burn of Hoffman-La Roche, a pharmaceutical company in Nutley, N.J.—have now made that speculation a reality.

All three groups popped the *obese* gene, either the mouse or a similar human version, into the genome of a bacterium and let the microorganism make large quantities of leptin. They injected this leptin, in various doses and at slightly different intervals, into the stomachs of different mouse strains.

Mice with the mutated *obese* gene, all three research teams report in the July 28 SCIENCE, ate much less when given leptin. In addition, metabolic changes indicate that they burned energy faster. The combination produced significant declines in body weight, almost exclusively from the loss of body fat.

Friedman's group, for example, reported that the obese mice given leptin lost around 30 percent of their body weight. Treated mice had, on average, around 9 grams of body fat, while untreated ones had more than 38 grams. When injected with leptin, normal mice, which have up to 5 grams of fat, lost almost all of their body fat—about 12 percent of their weight.

Friedman's team also showed that leptin made by the human *obese* gene, though slightly different, caused the obese mice to lose weight. Moreover, the group detected leptin in the blood of normal mice and humans but not in the genetically obese mice, further evidence that those mice don't make the fat signal.

Helping establish that leptin acts directly within the brain, the Hoffman-La Roche group showed that the hormone decreases food intake among the obese mice when injected into areas from which it may cross the blood-brain barrier.

A different overweight mouse strain does not respond to leptin, researchers note. That result fits perfectly with the hypothesis that those mutant mice do not make leptin's receptor, the cell-surface protein that recognizes leptin and presumably receives its signal within the brain.

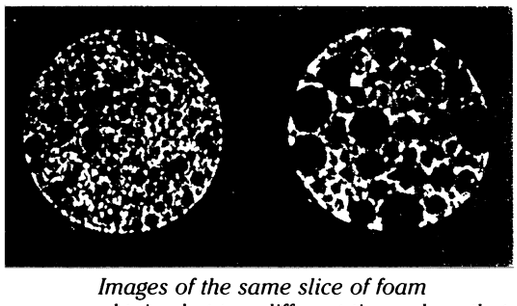
Debate rages over whether leptin will be useful in treating human obesity. "No one should expect that administration of this protein [to humans] will result in dramatic weight loss," argues José Caro of Thomas Jefferson University in Philadelphia. Caro's research suggests that human obesity may result not from an absence of leptin, but from problems in receiving its signals.

Other obesity researchers agree that finding the receptor will be a major advance but contend that there are not yet enough data to conclude whether leptin or its receptor is the best therapeutic hope. And before leptin is tested on people, investigators must establish that the hormone is not toxic to animals.

"They've only gotten to first base," says Timothy J. Rink of Amylin Pharmaceuticals in San Diego. "I think it will be many months before we get human data." —*J. Travis*

Probing the interior of a coarsening foam

Though made of gas pumped or swirled into a liquid, foams behave in ways that set them apart from their constituents. The lather of a shaving cream, for example, doesn't flow as readily as water or disperse as easily as air, and it can maintain its bubbly structure for lengthy periods of time.



Gonatas *et al.*

Images of the same slice of foam obtained at two different times show that larger bubbles appear later (right), though smaller bubbles persist.

Despite the widespread use of foams in applications ranging from oil recovery to firefighting, the details of their three-dimensional structure and flow characteristics are poorly understood. Researchers have had difficulty probing foam interiors without disturbing the bubbles or measuring just average characteristics (SN: 3/30/91, p.207).

Now, a team of physicists has demonstrated that magnetic resonance imaging (MRI) shows promise as a tool for studying a foam's internal structure and tracking changes in the size and number of bubbles present as a foam gradually drains. Using a sequence of such images, the researchers can begin to reconstruct the way in which a foam coarsens as some bubbles enlarge, while others shrink and disappear (SN: 7/29/89, p.72).

C.P. Gonatas and Arjun G. Yodh of the University of Pennsylvania in Philadelphia and their collaborators describe the technique in the July 17 PHYSICAL REVIEW LETTERS.

The researchers whipped up a special gelatin foam, which evolved slowly enough to allow them to use a medical MRI spectrometer to capture a sequence of images of the foam's interior. Each image corresponded to a two-dimensional slice through the thick, nearly solid material (see illustration).

"We did lots of slices through the same sample," Yodh says. "If you look at the same slice at different times, you can roughly follow the bubble changes."

"This is a step toward three-dimensional reconstruction," he notes. The researchers are also interested in improving the image resolution and increasing the data acquisition rate to monitor rapid structural changes. —*I. Peterson*