

OBESITY RESEARCH

Fat Hormone Makes a Comeback

Like frustrated dieters, obesity researchers sank into bitter disappointment 2 years ago when the scales tipped against leptin as a potential weight-loss drug. The hormone, produced by fat cells, normally quells appetite and balances the body's supply of fat and energy. But when given to dieting, obese individuals in a clinical trial, leptin supplements had little effect except in a fraction of those people given the highest doses (*Science*, 29 October 1999, p. 881).

But a new study has renewed researchers' hopes for leptin's potential as a pound-shedding drug. Endocrinologist

Stephen O'Rahilly of Addenbrooke's Hospital in Cambridge, U.K., and colleagues identified 13 people with defects in one copy of their leptin gene. These individuals make roughly half the normal levels of the hormone. Apparently as a result, they end up heavier and packed with a significantly higher percentage of body fat than family members with two normal copies of the leptin gene. The study suggests that at least in some people, low leptin levels—a treatable condition—can lead to obesity.

The results come as a surprise to many obesity researchers, who accepted the dogma that even a little bit of leptin was enough to regulate fat stores normally. "We now know that having a little less than the normal amount of leptin is enough to cause a problem with body fat and weight," says obesity researcher Jeffrey Flier of Beth Israel Deaconess Medical Center in Boston.

To pinpoint genes that confer excessive body fat, O'Rahilly spent 10 years gathering a cohort of extremely obese individuals with body mass indices (BMIs, defined as weight/height²) of at least four times higher than normal. The team first hit the jackpot in 1997 with a publication describing two Pakistani cousins who carried defects in both copies of the leptin gene. The cousins—and several other people subsequently identified—produced virtually no leptin and showed the hallmarks of leptin deficiency first discovered in 1994 in mice: excessive body fat, extreme hunger,

and sterility. But the children's parents weren't grossly obese, even though each carried one defective and one normal copy of the leptin gene. The conclusion, recalls O'Rahilly, was that leptin must operate under a threshold: "If you go from zero leptin to a smidgen, that is all you need" for normal fat metabolism, he says.

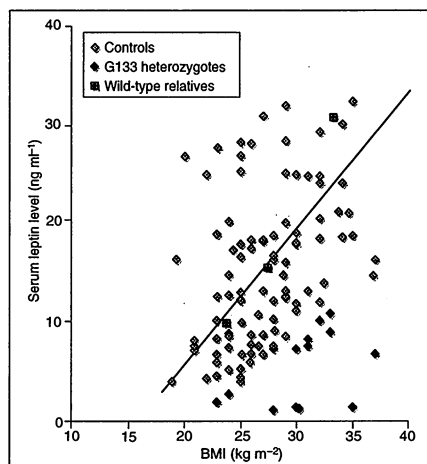
On the clinical front, the threshold theory explained why leptin apparently didn't work when given to most obese individuals. Most carry normal leptin genes, and many, in an apparent paradox, actually make higher than normal amounts of leptin—they just don't respond to the hormone properly. "So taking someone with leptin amount x and making it x -plus-something doesn't seem to make much of a difference," O'Rahilly explains—or at least, it didn't appear to make a difference until now.

The new study, based on three unrelated families, two in the U.K. and the third in Canada, calls this received wisdom into question. Some members of these families carry a mutation in at least one copy of the leptin gene, decreasing—to varying degrees in different family members—the amount of leptin their bodies produce. Most are

heavy but not grossly obese. The team measured the volunteers' blood leptin levels, BMI, and percentage of body fat. The lower the leptin level, the higher the BMI and percentage body fat, the researchers report in the 1 November issue of *Nature*.

People with both leptin genes knocked out respond "extremely well" to therapy, says O'Rahilly, who is preparing results for publication. Leptin injections damped down appetite, caused people to lose weight, and apparently spurred the onset of puberty. No similar assessments could be made with the new cohort of individuals with a single-gene defect: All refused leptin treatment. "These people are from a culture that considers it a status symbol to be chubby," he explains. But he suspects that some chubby people—with or without a leptin gene defect—who would prefer to slim down might benefit from the research. As O'Rahilly says, "There might be an obese subgroup with equivalently low leptin levels, which at least might be worthy of a clinical trial."

—TRISHA GURA



Weighty conclusion. Leptin levels do correlate with body mass, at least in some people.

new program, USDA would implement an active surveillance program, pay farmers a fair price for their animals, and also pay for destruction of the carcasses and decontamination of their farms.

By acting rapidly, says Creekmore, USDA hopes to control the CWD outbreak. It's not going to be cheap. For one thing, the soil in affected farms may have to be scraped off and decontaminated at high temperatures. But, she adds, "if we decide to wait, it will be a much more costly problem 10 years from now." —MARTIN ENSERINK

PHILANTHROPY

Caltech Lands Record-Breaking \$600 Million

Semiconductor pioneer Gordon Moore and his wife Betty set a new record in philanthropy last week by announcing a \$600 million donation to Moore's alma mater, the California Institute of Technology (Caltech) in Pasadena. The largest gift ever to a university, the money may fund everything from items on Caltech's wish list to projects not yet determined. The gift easily tops two other record-breaking university donations this year: \$400 million to Stanford University and \$360 million to Rensselaer Polytechnic Institute.

Moore earned a chemistry Ph.D. in 1954 from Caltech, a science and engineering powerhouse with 900 undergraduates and 1000 graduate students. He and a colleague went on to design the first microprocessors and found Intel, based in Santa Clara, California. Half of the Moores' \$600 million gift will be disbursed over 10 years by the Gordon and Betty Moore Foundation, established a year ago to fund environmental, science, and education projects. The foundation will fund mutually agreed-upon programs with "measurable results," Moore says. The other \$300 million, spread over the next 5 years, will be unrestricted.

Moore says he was motivated by his "long association with Caltech" and his belief that the school "fulfills a unique position in the country" that's an "expensive endeavor." Caltech president David Baltimore calls the donation "wonderful."

Baltimore says the money likely won't be used to expand the campus or "move in new directions." Instead, he expects it will strengthen existing research, which ranges from plate tectonics to postgenomics biology. The funds may also be used to upgrade facilities and "help faculty realize their research dreams." Caltech, he says, has a wish list that includes ideas such as a 30-meter optical telescope with the University of California. Money may also go to endowed professorships and the university's \$1.5 billion endowment. —JOCELYN KAISER