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The obsession with obesity

The moment when Jeffrey Friedman, of the Rockefeller University in New York, knew he had achieved a certain measure of celebrity came last December, shortly after his group had announced in *Nature* the cloning of the mouse *obese* (*Ob*) gene[1]. In the days following Friedman's numerous television appearances to discuss his team's discovery, he found himself making eye contact on the streets of New York to see if anyone would recognize him. Nobody did, until finally, on the upper east side, he was berated by a drunken panhandler who had seen him on television the previous night.

It would be interesting to record that gentleman's reaction now, following another blast of publicity in the wake of the recent reports from the Rockefeller group and researchers at Amgen and Hoffman-La Roche that mice injected with the recombinant mouse or human OB protein show marked reductions in weight — as much as 40% in the case of obese mice — over the course of just a few weeks[2–4]. Friedman's group has dubbed this potent 167-amino-acid protein 'leptin', from the Greek root *leptós* ('thin'). These dramatic results are ripe with potential implications for human therapeutics — Amgen is willing to stake almost $100 million for the rights to leptin. They also represent a belated but much deserved vindication of the pioneering work of Douglas Coleman at the Jackson Laboratory in Bar Harbor, Maine, some 25 years ago. Coleman, who retired in 1991, carried out the ghoulish parabiosis experiments, in which the bodies of different mice were experimentally joined together so as to exchange about 1% of their circulation. In this way, Coleman showed for example that *ob/ob* mice lost weight when parabiosed to wild-type mice, but would starve to death (as do wild-type animals) if physically joined with *db/db* mice. Coleman speculated that *ob* mice are defective in a normal circulatory factor which supresses appetite, but that *db* mice probably produce copious amounts of the protein, but are unable to respond to the factor themselves.

Douglas Coleman (left), Jeffrey Friedman and friend (an *ob* mouse), at the Jackson Laboratory last July. (Coleman was bitten by the mouse shortly after this picture was taken.)

Since the identification of the *ob* gene last year, two other important mouse genes linked with obesity and diabetes have been cloned. Researchers at the Jackson Laboratories identified the *fat* gene[5], which turns out to be the insulin processing enzyme, carboxypeptidase E. More recently, a team at Millennium Pharmaceuticals in Cambridge, Massachusetts, announced that they had isolated the *tubby* gene, which produces a form of obesity in mice considered very similar to that in humans in terms of onset and fat distribution. No scientific details about the *tubby*

work have been reported so far, but last month the company issued a press release, aimed squarely at the business community, disclosing that it had received a pre-arranged bonus payment from their corporate partner, Hoffmann-La Roche, following its success.

Together with the previous identification of *ob* and *agouti*, that leaves just one important monogenic cause of obesity in mice to be identified — *diabetes* (*db*), which produces a similarly severe phenotype as *ob*. At a recent meeting at the Jackson Laboratories, Friedman reported that his group had narrowed the region on mouse chromosome 4 containing *db* to just 300 kilobases or so. Whether the gene, which is thought to encode the receptor for leptin produced bythe fat cells, is ultimately identified by positional or expression cloning, the wait will not be too much longer.

Although progress in mouse models of obesity has been spectacular, the question remains as to what genetic components can trigger the condition in humans. The matter is of immense public interest, given that, for example, one in three Americans are said to be overweight, leaving them at heightened risk for a variety of medical ailments. Six months after Friedman's discovery, Jose Caro and colleagues at Thomas Jefferson University reported that the *ob* nonsense mutation was not present in the human homologue in five obese subjects, but its levels of expression were markedly elevated in obese patients[6]. Friedman says that his team has looked at more than 100 obese patients, and failed to detect any mutations in the leptin coding region. But this is not necessarily surprising, for only a handful of insulin mutations have been uncovered, yet no one can doubt the crucial importance of the hormone in diabetes.

New evidence about the precise sites of *OB* expression appear in this month's issue of *Nature Medicine*[7,8]. In one report, *obese* mRNA levels are shown to be greatly increased in omental and subcutaneous fat cells taken from massively obese individuals. One intriguing interpretation of these results is that the increased expression of leptin message stems from an inactive receptor in the hypothalamus — at least in some patients. Whether such reductionist thinking has any merit should become evident in the next few months.

Even as the exciting results on injecting leptin into mice are being digested, new reports have surfaced on the association of a possible genetic mutation in humans prone to non-insulin-dependent diabetes and obesity. In three reports

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Alternative treatments for fat mice. Many mice have simply changed their wardrobes.' Drawing by R. Chast; © 1995 *The New Yorker* Magazine, Inc.

in *The New England Journal of Medicine*[9–11], Alan Shuldiner of Johns Hopkins University and others show that a Trp64Arg missense mutation in the β3-adrenergic receptor is associated with earlier onset NIDDM and increased body weight in Pima Indians in Arizona and populations from Finland and France. The researchers also found that the β3-adrenergic receptor variant was associated with lower resting metabolic rate, resistance to insulin and, in the Finnish study, 'an increased ratio of waist to hip circumference' — a 'pot belly' in other words. This receptor has an important role in mediating thermogenesis in brown fat, stimulated by catecholamines, as well as stimulating lipolysis in white fat cells. By analogy with other G-protein coupled receptors, the missense mutation, which occurs at the base of the first membrane-spanning region of the receptor, might result in impaired cellular trafficking of the protein, thereby compromising thermogenesis and lipolysis, leading to diabetes and related disorders. It will be interesting to see whether this pathway and that involving leptin have anything in common. However, drug companies are not waiting to find out: they are pursuing all of the new clues about obesity, realizing full well that it is not just clinically obese who will be interested in the prospect of a guaranteed weight-loss programme.

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