eron Pharmaceuticals in Tarrytown, New York, started experimenting with axokine, a patented derivative of CNTF. When they made normal rodents obese by putting them on a high-fat diet, the animals became resistant to leptin. But when the researchers injected these same animals with axokine, the rodents shed 30 per cent of their body weight and maintained their moderate eating habits, even several days after their last injection.

## Sights set on success

Last September, Regeneron completed a phase I clinical trial of axokine. Although at high doses the drug seemed to cause cold sores and nausea, patients tolerated low doses well. The results have yet to be published, but most patients lost significant amounts of weight, reducing their energy intake by about 500 calories a day. Yancopoulos calls axokine "the most promising weight loss agent ever described", but others are more cautious. Tartaglia at Millennium, for example, worries that tinkering with a neuronal growth factor could have delayed effects that are difficult to predict.

Despite its disappointing performance so far, leptin itself is still the focus of interest from drug developers. Many scientists, including those from Amgen, think leptin might help people maintain weight loss. For most people, the hardest part of dieting is not shedding weight, but keeping it off — they tend to return to their previous weight. The drop in the level of circulating leptin is probably partly to blame for this because the ensuing shrinkage of fat cells sounds a 'starvation alarm' that boosts the appetite. Leptin injections could help overcome this by fooling the brain into thinking that its energy stores are not at risk.

Amgen is also designing second-generation versions of leptin. The goal is to make leptin mimics that are more soluble — to increase the dose that can be injected into patients — and more stable, to last longer in the bloodstream. Other researchers are designing small molecules with leptin-like activity that can easily cross the blood–brain barrier. This could be important, because the ratio of leptin in cerebrospinal fluid to that in blood is four times lower in obese people than in those of normal weight[17,18].

The success or failure of these strategies, however, depends on how leptin sensitivity varies from person to person. Because of their resistance to leptin, flushing the cerebrospinal fluid of obese people with leptin-like molecules might make very little difference. So Amgen is searching for biomarkers that correlate with leptin sensitivity. This may allow leptin to be prescribed selectively to those who are likely to respond more strongly to the hormone.

Leptin's reach may also extend to the treatment of other, related diseases. Roger Unger at the University of Texas Southwestern Medical Center in Dallas believes that obesity-induced diabetes develops when pancreatic β-cells die after accumulating excessive fat in their cytoplasm. By stimulating receptors on the surface of β-cells, Unger thinks leptin can stop this from happening. But other researchers caution that leptin's interaction with insulin remains mysterious and controversial.

While Amgen's multimillion-dollar bet on leptin doesn't look like yielding an immediate bonanza for the company, obesity researchers agree that the protein has kick-started an exciting field — both for basic research and for drug development. "Whatever has happened to leptin as an immediate therapeutic tool, as a discovery that sparked an area of biomedical research, it's phenomenal," says O'Rahilly. ■

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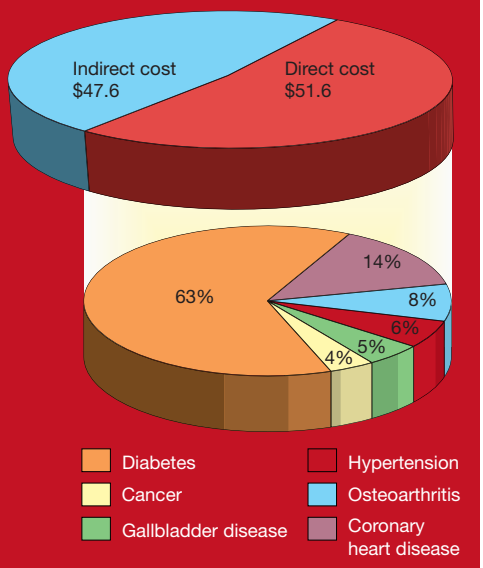
ERIC SANDER/LIAISON AGENCY

**Diet plan: Amgen still believes leptin is the key to the lucrative obesity market.**

## Counting the cost of obesity

For the first company to bring a potent weight-loss drug to the market, the rewards could be huge. Across the industrialized world, the prevalence of obesity is rising. Last month, the Worldwatch Institute in Washington DC reported that 1.1 billion people worldwide are now suffering from the health consequences of overconsumption — equal to the number plagued by hunger. In the United States alone, where more than one in three adults is classified as obese, the condition is estimated to cause 300,000 premature deaths each year. And, as these figures reveal, the associated burden of disease causes a significant annual dent in the US economy — both from the direct cost of treating conditions triggered by obesity, and from lost economic productivity.




Source: Wolf, A. M. & Colditz, G. A., Obes. Res. 6, 97-106 (1998)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