an enzyme-catalyzed process to link the two amino acid moieties of the sweetener. However, as Osterhof points out, fermentation is still the major source of the phenylalanine used as a raw material both by HSC and by its competitors.

Biotechnology is also making other contributions on the "input" side of obesity. After decades of breeding dairy cattle to produce creamy, fat-rich milk, animal breeders are now starting to take the fat out again, a process that this time, thanks to modern embryo manipulation and transfer techniques, may take just a few years. Similarly, the use of porcine and bovine somatotropin reduces the fat content of meat. Enthusiasts might also point to the use of *Fusarium* spp. in the production of the fat-free meat substitute, Quorn, a kind of mycological tofu that is produced in multiton quantities by Zeneca BioScience (Billingham, U.K.). However, Quorn's reputation as a diet food is diminished by the fact that much of the product ends up in pastry encrusted vegetarian pies and similarly calorie-laden fare.

Tinkering with the Machine

Biotechnology's attempts to tackle the input side of obesity seem, however, largely to have come to naught. On average, people in developed countries are not getting less obese. The human body is not easily fooled—by chewing and swallowing—into thinking that it is nutritionally satisfied. Between 75 and 95 percent of all dieters fail to keep their lost weight off. Human weakness has usually been blamed.

But Tim Rink, president and chief technical officer at Amylin Pharmaceuticals (San Diego, CA), dismisses that notion. "Obesity is definitely not just the result of gluttony and sloth." As a physiologist, Rink has long maintained that because body fat in animals and humans does not change over long periods under changing environmental conditions, there must be powerful regulatory mechanisms at work. And the existence of those mechanisms means that intervention in order to treat obesity is highly plausible.

This is what the work at Rockefeller, Amgen, and Roche on the *ob* gene product, leptin, confirmed—at least in mice. In December 1994, Jeffrey Friedman's group at the Howard Hughes Medical Institute at Rockefeller University published a paper in *Nature*[6] announcing that they had cloned and sequenced the mouse *ob* gene. The *ob* mutation had been identified in 1950[7] and had subsequently been shown to be a single mutation that produces a phenotype-profound obesity and type II diabetes, which resembles morbid obesity in humans. In a series of carefully controlled experiments, the researchers have now shown that cloned leptin purified from *E. coli* induced weight loss in a dose-dependent manner both in obese mice, which are deficient in the protein, and in normal mice. But it had no effect on obese mice, which putatively lack a receptor for leptin. Importantly, leptin appears to both suppress appetite and increase fat-burning metabolism.

Is Leptin Critical?

But just how important is leptin? There are, after all, numerous existing drug development programs for obesity. Companies such as Hoffmann-La Roche, Merck (Rahway, NJ), and Abbott (Abbott Park, IL) have been looking at the peptide, cholecystokinin (CCK), and its analogs, as appetite suppressants for almost a decade. Serotonin, dexfenfluramine, neuropeptide Y, and agonists of the β_3-adrenoceptor are other candidates. And Amylin's eponymous product seems to exert powerful effects in animals on appetite, food intake, and even on weight, effects that the company's researchers will be looking out for in its imminent phase III clinical studies, even though the primary end-point for those trials is its effects on glucose metabolism.

Rink thinks leptin is very important. He goes as

Obesys has no full-time employees, a very small research and development budget, and no place it can call its own. And yet it expects to get to market before Amgen and Roche.

Fat Antibodies and Fat Cats

Davis Farmer believes that his company's treatment for obesity will be on the market years before leptin, its analogs, or any compound based on the molecular biology of obesity. "If we are ten years from the market, they are twenty years away." Farmer is president of Obesys, a U.K.-based virtual biotechnology company that owns intellectual property rights to a technique that has been described as "biochemical liposuction." Obesys has no full-time employees, a very small research and development budget, and no place it can call its own. And yet it expects to get to market before Amgen and Roche.

The company's technology, based on work in animals by David Flint at the Hannah Research Institute (Ayr, U.K.) is straightforward and direct. Antibodies—whether polyclonal, monoclonal, or fragments—specific for adipocyte plasma membranes, are injected directly into fatty tissue. A few days or weeks later, both the number and the size of the fat cells are significantly reduced. In animal experiments in rats, sheep, rabbits, pigs, and chickens, overall adipose tissue losses of up to 75% have been observed.

Within in the next 6-12 months, Farmer hopes to find corporate partners to develop the method both as a human therapy and as a treatment for obese pets. "As a virtual company with a core of intellectual property rights, what we do next is dependent on future partnering. We are proceeding with our own resources to develop human monoclonal antibodies."

Although all the work so far has been performed in animals, Farmer does not particularly see the veterinary application as a fast-track option. "There will be just as much effort involved in developing a treatment for fat cats as there will be for fat cat owners," he says. "But if you can build up a solid block of data and do some fine tuning in animals, the likelihood of acceptability in humans is greater."

If biochemical liposuction has advantages over a "fat pill," they are its speed and its longevity. "A couple of weeks, a couple of months," explains Farmer, "that appeals to me....If I'm a patient, I'd much rather go through a few weeks of treatment and achieve a lasting result." ///