Converting the calorific value to a figure of equivalent body mass, biotechnology's total annual contribution to obesity represents over 1000 million kilograms in weight gain avoided.

far as comparing its apparent role in fat metabolism with that of insulin in regulating glucose metabolism: "There are numerous mechanisms for regulating blood glucose but it's absolutely impossible to understand the regulation of glucose without understanding insulin. It forms the backbone of the regulatory system and the backbone of the diseases and their treatment. . . .The *ob* concept is the same—there may be several regulatory mechanisms working together but there is often one overarching or particularly fundamental one." He believes that it is extraordinarily likely that the *ob* system will prove to be central in developing therapy for human obesity.

Also trying to circumvent Amgen's intellectual property position through gene discovery is Millenium Pharmaceuticals (Cambridge, MA). The company has a broad five year collaboration in gene discovery with Hoffmann-La Roche, worth some $70 million to Millenium. Roche receives rights to develop small-molecule treatments for obesity and type II diabetes. Outside the U.S., Roche has rights to develop antisense, protein, and gene therapies, rights that Millenium has retained for the U.S.

In August, Millenium announced the cloning of *tub*, the gene responsible for the obese phenotype in the "tubby" mouse, and its human homolog. Thus far, however, Millenium has said nothing about the science behind the discovery: "*tub* is not *ob*—and it's not the *ob* receptor," is about as far as Steven Holtzman, Millenium's chief business officer was prepared to go. "What we announced was a business milestone that triggered a milestone payment from Roche."

Counting the Calories

High-fructose corn syrup is the product of an enzymatic conversion of corn starch to fructose and glucose, using a combination of glucose amylase and glucose isomerase. By 1986, over 5.5 million metric tons of HFCS were being used annually in the U.S. and just under 1 million metric tons elsewhere in the world. Three-quarters of the U.S. total was for the soft drinks industry. At that time, the glucose isomerase step in HFCS production was the largest scale use of immobilized enzymes. The economic benefits were large. By utilizing a surplus of maize starch, the U.S. alone saved some 3.7 million metric tons of sugar imports in 1980, worth, according to a U.S. government estimate, around $1.3 billion. The dietary benefits were perhaps less dramatic. HFCS 55, a formulation containing 55% fructose, which was widely used in soft drinks, is approximately 10% sweeter on a mass basis than the sucrose it replaced. A back-of-the-envelope calculation, therefore, reveals that HFCS may have contributed a reduction in worldwide carbohydrate-derived energy intake of around 2.6 million million kilocalories.

Any calculation of the contribution of biotechnology's other sweetener, aspartame to obesity has to struggle to overcome the paucity of hard market information on the compound. The virtual duopoly involving NutraSweet and Holland Sweet-ener makes the players involved wary of divulging even the most basic of market or technical information. The ferocity with which companies have fought for market share was well illustrated in the late 1980s when NutraSweet began importing the compound into Europe at prices far below those it was charging in the U.S. After protests from Holland Sweetener in 1991, the European Community imposed antidumping duties on aspartame coming into Europe, thereby slowing the incursion by NutraSweet and its partner Ajinomoto (Tokyo, Japan). Those duties are about to be lifted.

HSC's technical manager, Richard Osterhof, was, however, prepared to estimate that the total annual world production of aspartame is now 10-15,000 metric tons per year, of which HSC produces 2,000-2,500. Since aspartame is about 200 times sweeter than sucrose, the annual world reduction in calorific input—making the outrageous assumption that the compound substitutes directly for sucrose—is probably in excess of 8 million million kilocalories.

Converting the calorific value to a figure of equivalent body mass, biotechnology's total annual contribution to obesity represents over 1000 million kilograms in weight gain avoided—just over a kilogram per year per person in the developed world. ///

Tim Harris, senior vice president, research, and chief technical officer at Sequana Therapeutics (San Diego, CA) is reserving his judgment until some human data are in. He makes one obvious, but crucial, point. "If you have a mutation in the *ob* gene and you are a mouse, then you will be obese. But whether mouse *ob* genes tell you anything about obesity in humans, is an open question." Amgen has indicated that it hopes to begin clinical safety studies as early as 1996.

Looking Around, Getting Around

Meanwhile, Sequana plans to continuing looking for other obesity-associated genes in humans. Through its collaborators at the Institute Pasteur (Paris, France) and the University of Pennsylvania (Philadelphia), the company has access to what Harris believes is the best collection of morbidly obese families in the world. Although these people are clearly not typically obese, Harris believes that the use of the extreme phenotypes make the qualitative genetics of obesity easier to analyze.

Other *Ob*-vious Questions

Whichever factor or factors turn out to be important in human obesity, there is clearly a lot of work still to be done. Amylin's Rink says that "*ob* is 70 years behind insulin in getting established because we have only just been able to get hold of it. . . .We are where we were with insulin before 1921; all the animal experiments had been done but nothing had been demonstrated in humans."

Sequana's Harris agrees. "Even if the human