**Cellular Warriors at the Battle of the Bulge**

Researchers are picking apart the molecular signals the body uses to regulate its weight—work that may lead to new antioesity drugs

When Mae West said that too much of a good thing can be wonderful, she wasn’t talking about food. Over the past 50 years or so, food availability has soared, at least in the developed world, and too much food has turned out to be far from a good thing. That order of fries you buy in your local fast-food restaurant isn’t the only thing that’s become supersized in the United States: So has the national waistline.

By current estimates, 30% of U.S. adults are obese—roughly double the percentage 20 years ago—and another 35% are overweight. Children and adolescents haven’t been immune to this obesity epidemic; 15% are too fat. All this excess poundage is much more than an aesthetic issue; obesity is a major risk factor for such life-threatening diseases as type II diabetes (Science, 26 April 2002, p. 686), heart attack, stroke, and some types of cancer, including breast and colon cancers. Indeed, some 300,000 people die of obesity-related diseases every year in the United States alone.

But there’s a glimmer of hope. Researchers have learned a great deal about how the body regulates its weight. “We know that there are physiological systems in place that seem to be involved in maintaining weight,” says obesity researcher Jeffrey Flier of Beth Israel Deaconess Medical Center in Boston.

One of these systems is primarily concerned with short-term weight regulation—how often and how much we eat on a given day—and the other with longer-term regulation. Over the past few years, scientists have identified numerous components of each. Recently, for example, two peptide hormones produced by the digestive tract, known as ghrelin and PYY, have been linked to short-term feeding behaviors, whereas leptin, and to a lesser extent, insulin, are key to weight maintenance over months and years.

Obesity researchers have also made progress toward understanding how these hormones exert their effects. Among other things, they’ve found that certain brain regions, such as the arcuate nucleus, play a critical role in integrating the hormones’ activities, sending signals that tell the body to adjust its food intake and energy expenditure. “A coherent wiring diagram can now be drawn” showing how these hormones work, says leptin discoverer Jeffrey Friedman of Rockefeller University in New York City.

The pharmaceutical industry has been having great difficulty coming up with antiobesity drugs that are both safe and effective (see p. 849), but the wealth of information now being gained should provide several new drug targets.

In one regard, though, the message coming out of this work is depressing for people who want to lose weight: The body’s weight-control systems have apparently been designed to protect more against weight loss than weight gain (see Friedman Viewpoint on p. 856). That undoubtedly reflects human evolutionary history in which, until very recently, food scarcity, not overabundance, was the danger. As geneticist Rudolph Leibel of Rockefeller University in New York City says, “You can bemoan the fact that we’re set up this way, but it’s what’s gotten us here.”

**Long-term savings**

The discovery that helped kick off the current surge of obesity research was the Friedman team’s identification of leptin in 1994. Interest in the area “exploded” as a result, says geneticist Stephen O’Rahilly of the University of Cambridge, U.K.: “It was the first [anti-obesity] hormone you could get your hands on.”

Friedman and his colleagues found leptin by tracing the gene at fault in a mutant strain of extremely obese mice and went on to show that they could cure the animals’ obesity by treating them with the hormone. It produced weight loss by decreasing the animals’ appetite while at the same time revving up their metabolic rates. As humans have their own version of the leptin gene, the results grabbed everyone’s attention. Would leptin prove to be the “magic bullet” that would cure the ever-growing human obesity problem?

Those hopes were soon dashed. Some rare cases of human obesity are caused by defects in leptin production. O’Rahilly, Sadaq Farooqi, also at Cambridge, and their colleagues have recently used leptin to treat three children who were extremely obese because they don’t make the hormone. The children’s weights quickly dropped, mainly because they ate much less than before, the researchers reported in the October 2002 Journal of Clinical Investigation. “Although leptin deficiencies are rare, they are treatable,” O’Rahilly says.

But unlike such patients and the mutant mice, most obese humans turned out to have higher than normal blood levels of leptin, which is produced by fat cells. For reasons not yet understood, they are resistant to its actions. That’s one reason why many obesity researchers now think that leptin’s main role is protecting against weight loss in times of deprivation rather than against weight gain in
times of plenty.

When a person’s fat stores shrink, so does leptin production. In response, appetite increases while metabolism decreases. But the converse does not happen. Beyond a certain point, increased leptin production does little to inhibit appetite or increase metabolism. “The neurons of the arcuate nucleus, which was already known to be involved in appetite regulation, carry relatively large amounts of the receptor and might thus be prime targets for leptin in the brain.

Since then, numerous labs have traced the neuronal pathways through which leptin works in the brain and have shown that other hormones involved in weight control often work through the same pathways. Particularly important is the arcuate nucleus, which Friedman describes as the “master center: the seat of both the short-term and long-term [weight-regulatory] systems.”

The arcuate nucleus, which is located in the hypothalamus, contains two major types of neurons with opposing actions. Activation of one type, which produces peptide neurotransmitters called neuropeptide Y (NPY) and agouti-related peptide (AgRP), stimulates appetite while reducing metabolism. In contrast, activation of the other type, known as POMC/CART neurons, causes the release of α-melanocyte-stimulating hormone (α-MSH), which inhibits eating.

When fat stores and leptin levels are declining, the NPY/AgRP neurons are activated and the POMC neurons are inhibited, leading to weight gain. Conversely, at least in nonresistant animals, increasing fat stores and leptin levels lead to inhibition of the NPY/AgRP neurons and activation of the POMC neurons, resulting in weight loss. The NPY/AgRP and POMC/CART neurons then send their signals through certain other brain centers to the nucleus tractus solitarius of the brain stem, and from there to the rest of the body.

One indication of the importance of these circuits for weight control comes from O’Rahilly and Farooqi and also from Philippe Froguel’s team at the Institute of Biology in Lille, France. Although very few cases of human obesity have been linked to mutations in either the leptin or leptin receptor genes, these researchers showed a few years ago that mutations in the receptor through which α-MSH exerts its appetite-inhibiting effects are much more common, accounting for perhaps 5% of severe obesity cases. Researchers are now looking for compounds that can be used to activate the receptor in obese people who don’t carry such mutations.

Additional targets for potential antiobesity drugs come from work in which researchers have been pinning down the mechanisms by which leptin turns up the body’s metabolism. It apparently does this at least partly by altering the pathways through which fat is metabolized. For example, in work reported in Nature in January 2002, Barbara Kahn’s team at Beth Israel found that leptin activates a so-called kinase enzyme in muscle that inhibits acetyl coenzyme A carboxylase, an enzyme that catalyzes a key step in fat synthesis.

As a result, the building blocks that would otherwise go into fat formation are shifted into a pathway that oxidizes them, providing energy for muscle cells. “We didn’t say [in the paper] that this causes lean-ness,” Kahn says, “but it probably does. If an animal oxidizes its fatty acids instead of storing them, it is going to be leaner.”

Although leptin is not very effective for treating garden varieties of human obesity, its discovery did open the door to a better understanding of the body’s weight-control mechanisms. Shortly after the Friedman group discovered the hormone, a team led by Louis Tartaglia of Millennium Pharmaceuticals in Cambridge, Massachusetts, found the gene for the receptor through which leptin exerts its effects. From there, researchers were able to show that the neuronal pathways through which fat is metabolized.
Results from Friedman and his colleagues suggest that something similar may happen in the liver, although there is a different enzyme, stearoyl-CoA desaturase-1 (SCD-1), involved. The Rockefeller team has evidence that leptin exerts its antiobesity effects by turning down the activity of the SCD-1 gene. They found that they could protect leptin-deficient mice from obesity by inactivating the SCD-1 gene. The animals also had much higher metabolic rates than ordinary leptin-deficient mice, and their livers stored less fat. In some way the researchers don’t yet understand, Friedman says, turning down SCD-1 activity fosters fat metabolism.

**Insulin revival**

Although leptin has received the lion’s share of attention as an appetite and metabolism regulator, there are other players, and some of them also work through the arcuate nucleus. For example, some 25 years ago, Daniel Porte of the University of California, San Diego, and Stephen Woods of the University of Cincinnati suggested that the hormone insulin acts through the brain to regulate weight. Interest in the idea waned somewhat after the discovery of leptin, but recent work is reviving it. “Insulin is definitely having a comeback,” Flier says.

Some of this evidence comes from Ronald Kahn (no relation to Barbara Kahn) and colleagues at the Joslin Diabetes Center in Boston. They stymied insulin action in the brains of mice by knocking out the insulin receptors located there and found that the animals overate and became fat (Science, 22 September 2000, p. 2122).

Insulin receptors occur throughout the brain, but other work has tied the hormone’s appetite-suppressing action directly to the arcuate nucleus. Insulin infused into the brain near the arcuate nucleus inhibits production of the appetite-stimulating NPY, researchers such as Michael Schwartz of the University of Washington, Seattle, have found. And when Luciano Rossetti’s team at Albert Einstein College of Medicine in New York City inhibited production of the insulin receptor specifically in the arcuate nucleus of mice, the animals immediately increased their food intake, the team reported in the June 2002 issue of Nature Neuroscience. As Schwartz puts it, “as long as the brain has normal insulin sensitivity, you eat less and lose weight.” He and others note, however, that insulin’s effects in this regard aren’t as strong as leptin’s.

Related studies may lead to antiobesity drugs that could circumvent obese people’s resistance to the hormones’ effects. For instance, in experiments described in the April 2002 issue of Developmental Cell, Barbara Kahn, Benjamin Neel, also at Beth Israel, and their colleagues knocked out an enzyme called protein tyrosine phosphatase 1B (PTP1B) in mice. The animals gained much less weight when fed a high-calorie diet than did normal controls. This apparently happens because the enzyme inhibits leptin and insulin signaling in the hypothalamus and other brain areas. Thus, it may be possible to bolster the hormones’ effects with a PTP1B inhibitor. Barbara Kahn says the enzyme is a “terrific drug target. Other than being lean,” she says, “the mice are pretty normal.”

**Short-term appetite control**

In addition to getting a handle on how the body regulates appetite and metabolism over the long haul, obesity researchers are gaining a better understanding of how it controls appetite on a daily basis. Several years ago, they identified cholecystokinin, a peptide released into the bloodstream by the intestine, as a “satiety hormone”—one that tells us when we’ve had enough to eat. Two recently identified appetite-regulating hormones are now attracting attention, both scientifically and from the drug-development point of view. These are ghrelin, an appetite stimulant, and PYY, a suppressant.

Kenji Kanagawa, Masayasu Kojima, and colleagues at the National Cardiovascular Center Research Institute in Osaka, Japan, discovered ghrelin, a peptide produced by the stomach, about 3 years ago. They found that it causes the release of growth hormone by the pituitary gland. About a year later, however, Matthias Tschöp, then at Lilly and colleagues discovered that the hormone has another function as well: It’s a “meal initiator,” because fat stores don’t seem highly unlikely that leptin could be a “meal initiator,” because fat stores don’t drop between breakfast and lunch. But ghrelin seems to fit the bill.

For example, when Stephen Bloom of the Imperial College Faculty of Medicine in London and his colleagues injected ghrelin into human volunteers, it had “an amazing, very powerful” effect in increasing the amount of food they subsequently ate, he says. In
Obesity Drug Pipeline Not So Fat

Eating right and exercising be damned; the search is on for drugs that can control obesity

Drugmakers have been salivating over the prospect of creating antiobesity medications. Obesity is a rising pandemic that includes 60 million adults in the United States alone, and although most physicians champion diet and exercise as the best way to fight fat, many people are desperate for an easier way to avoid corpulence and consequences such as heart disease, stroke, and diabetes. It’s a drugmaker’s dream.

Prospects looked good in 1994 when the discovery of the fat-regulating hormone leptin blew open the doors to the molecular world of obesity. The discovery promised researchers a colorful vista of new strategies to work with. They are badly needed; only three fat-busting drugs have clawed their way into the marketplace and held on—amid lawsuits, severe side effects, and even, possibly, deaths.

Why aren’t there more antiobesity drugs? Quite simply, “it’s hard to treat complex diseases,” says George Yancopoulos, chief scientific officer and president of Regeneron Laboratories in Tarrytown, New York. Such drugs must tamper with the biochemistry of metabolism; it’s an essential system for survival and thus sometimes fatal to disrupt. In addition, appetitive circuits in the brain use neurotransmitters and receptors that control other body processes. “If you target these things, you can get terrible side effects,” says endocrinologist Stephen Bloom of the Imperial College Faculty of Medicine in London. And that has been the story as obesity pill after hyped obesity pill has come to market.

And yet research, postleptin, is yielding important insights into the body’s cast of calorific characters (see p. 846). Some discoveries are nearing the end of the drug-development pipeline, enduring the decade-long time scale of pharmaceutical research and testing. Others are in early clinical trials. More are likely to follow; for example, two hot new molecules appear to influence short-term eating patterns. “Even if today obese individuals or health-care providers are frustrated,” says Michael Schwartz of the University of