addition, Cummings and his colleagues, including Puget Sound's Brent Wisse, found that ghrelin levels rose an hour or two before a meal and went down to trough levels afterward—"exactly what was predicted" for a meal initiator, Cummings says. Ghrelin may stimulate appetite by working through the arcuate nucleus, as researchers have found that it activates the NPY/AgRP neurons there.

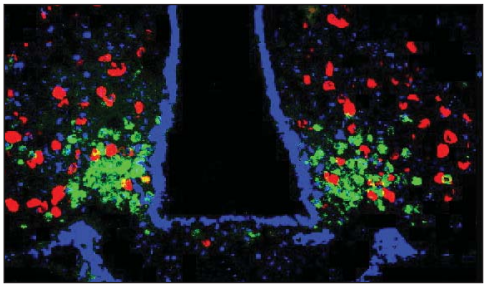
Although ghrelin is part of the short-term appetite-control system, it can, if overproduced, lead to obesity. Prader-Willi syndrome is an inherited condition that causes its victims to be extremely obese—so much so, Cummings says, that they often die before age 30 of obesity-related diseases. The Seattle team found that the patients have what Cummings describes as the "highest ghrelin levels ever measured in any humans," although the increased ghrelin production is apparently an indirect effect of the other chromosomal abnormalities underlying the disease.

Prader-Willi syndrome is rare, and most obese humans tend to have lower ghrelin levels than people of normal weight, but there is another way in which the hormone may contribute to obesity. The Cummings team reported in the 23 May issue of *The New England Journal of Medicine* that ghrelin production increased in people who had lost weight through dieting. The hormone may thus be part of the mechanism that undermines a dieter's ability to shed pounds.

Not every form of weight loss causes ghrelin production to go up, however. An operation called gastric bypass, which involves taking a small portion of the upper stomach and reconnecting it to the small intestine, seems to be an effective way of treating extreme obesity. Cummings and his colleagues have found that, for reasons not yet understood, ghrelin levels go down—and stay down—in people who have undergone the surgery. This might be why they don't try to compensate for their smaller stomachs by eating more frequently.

Meals have to be terminated as well as initiated. And recent work by Bloom's group, in collaboration with that of Roger Cone of Oregon Health and Science University in Portland, shows that PYY has an important role to play in that regard. The researchers reported in the 8 August 2002 issue of *Nature* that infusions of the hormone lead to decreased eating by mice, rats, and human volunteers. The hormone acts in the arcuate nucleus, in this case inhibiting the activity of the appetite-stimulating NPY/AgRP neurons and stimulating the appetite-suppressive POMC cells.

Whether this recently accumulated knowledge about the body's weight-control systems will pay off in better antiobesity treatments remains to be seen. But if it does, both epidemiology and a new experimental study suggest that the reward may be large: a longer life. In addition to lowering one's risk of deadly obesity-related diseases, calorie restriction can extend the lifespans of organisms ranging from the fruit fly to rodents.



Central command. In the arcuate nucleus, NPY/AgRP neurons (green) and POMC/CART neurons (red) fight for control of feeding behavior.

Exactly why this is so is not clear. But in the 24 January issue of *Science* (p. 572), Ronald Kahn, with Barbara Kahn and Matthias Blüher, also at the Joslin Diabetes Center, report that leanness alone may be all it takes. In earlier work, the Boston workers had genetically modified mice so that their fat cells do not make insulin receptors. Those animals have 50% to 70% less fat than unaltered mice, but they otherwise appear healthy.

In the new work, the researchers found that the median life span of the modified mice increased from about 30 months to 33.5 months. Because these animals, despite their leanness, actually eat more than normal mice, the Boston group concludes that the decreased fat tissue produced by calorie restriction, rather than the sparse food intake itself, is what's important for greater longevity. Given how hard it is to lose weight, keeping a life-span perspective in mind might help us resist adding new pounds. **–JEAN MARX**

NEWS

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, appetite 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 caloric 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

CREDITS: (TOP) TO BOTTOM) DENNIS BASKIN/VETERANS AFFAIRS PUGET SOUND HEALTH CARE SYSTEM; PHOTODISC

Washington, Seattle, "targets that exist now have the potential to lead to real breakthroughs in the future."

Unappetizing options

The current trio of drugs on the market, endocrinologists say, is, at best, weak and, at worst, plagued by side effects. Hoffmann–La Roche's Xenical, for instance, blocks fat-digesting enzymes called lipases. That prevents the gut from digesting and absorbing fat. But lipids aren't the only molecules malabsorbed; Xenical also causes cramping and severe diarrhea in many obese patients because water molecules also fail to be taken up by the gut.

What's more, the drug often doesn't work well. "The weight reduction after a year of Xenical is exactly equal to the weight of the number of Xenical tablets you have taken," Bloom quips. A metanalysis of Xenical trials showed that the drug helped dieting patients lose an average of 2% to 3% of their body weight as compared to those dieting alone. Often patients gained the weight back after discontinuing the drug. Physicians say they are not surprised that Xenical sales fell 17% in the first 9 months of 2002 as compared to the same time frame the previous year, according to company figures.

Abbott Laboratories' Meridia (called Reductil in Europe) has encountered more serious problems, provoking a class-action lawsuit, a U.S. Food and Drug Administration (FDA) investigation, and a withdrawal from Italian markets. Meridia, or sibutramine as chemists and researchers know it, belongs to a family of amphetamine-like compounds. The drug hinders molecules at synapses that pick up the neurotransmitters noradrenaline and serotonin after they've been discharged by a neuron. But because the two chemical signals also control a myriad of other body processes, side effects ensue. "It's not surprising" that a drug in this family raises blood pressure, for example, says Sidney Wolfe, director of the advocacy group Public Citizen.

Between February 1998 and September 2001, 150 patients taking Meridia worldwide were hospitalized and 29 died, 19 from cardiovascular problems. In March 2002, Public Citizen petitioned FDA to withdraw the drug from the market. The group cited evidence from prior clinical trials that the drug increases blood pressure. FDA is now conducting an investigation. The Italian government has already acted: It pulled the drug from pharmacies in March 2002 after two patients died.

In a press release issued the day after Public Citizen's petition, Abbott responded that the death rate among patients taking the drug (12,000 in clinical trials and 8.5 million patients worldwide) was "substantially lower" than what would normally occur in any obese patient population. The company's arguments received a boost in June 2002 when the European Union's Committee for Proprietary Medicinal Products, responding to a request from the Italian Health Ministry for a review, concluded that the benefits outweigh the risks. But the drug has not yet been reinstated in Italy, and the ministry has vowed to continue its review of the drug.

Further supporting the usefulness of Meridia and Xenical, a December 2002 study by Andre Scheen's group at CHU Sart Tilman in Liege, Belgium, showed that obese patients who had achieved weight loss with either drug showed significant declines in factors associated with risk for diabetes, such as insulin resistance and glucose intolerance. The authors called for long-term studies to test whether the risk reduction holds up with time.

That leaves the 53-year-old generic drug phentermine—one-half of the infamous fen-phen combination (a.k.a. Redux) that caused heart problems, deaths, and litigation that eventually cost its manufacturer, Wyeth-Ayerst Laboratories, $13.2 billion. In part due to a Public Citizen petition, FDA in 1997 banned the "fen" component, fenfluramine, which targets the release of serotonin and has been linked to heart valve disease. As it stands, says Yancopoulos, "obesity is the most dangerous epidemic facing mankind, and we are relatively unprepared for it."

On a future menu

Two antiobesity drugs that might outperform today's contenders have reached late-stage clinical trials. Researchers at Sanofi-

Having It All

It's the perfect drug for a midlife crisis: Lose weight, get a tan, and boost your sex life, all in one pill. The target for the drug is melanocortin receptor–1 (MCR-1), discovered in a mutant mouse called *agouti* that is fat and bears a coat of shockingly yellow fur (*Science*, 7 February 1997, p. 751). The mutated protein binds to MCR-1 in the mouse's skin and hinders the production of black pigment. The agouti protein also blocks other melanocortin receptors, MCR-3 and MCR-4, that quell feeding.

Dermatologist Norman Levine of the University of Arizona in Tucson wanted to activate MCR-1 with a drug that might cause tanning and thus protect patients against ultraviolet-light damage. But in studies in people, Levine noticed that men taking the drug, dubbed Melanotan II, consistently got unexpected erections. He passed the news along. Eventually, the university licensed the compound to a biotech company called Palatin Technologies in Cranbury, New Jersey. Researchers tinkered with the drug and came up with PT141, a metabolite of Melanotan II.

In phase I and II trials, 310 men taking the drug have shown promising results. Volunteers looked at racy magazines and videos while hooked up to a device called a rigiscan that measures, well, rigidity. PT141 boosted that quality within 30 minutes of swallowing the pill. (Viagra takes about an hour.)

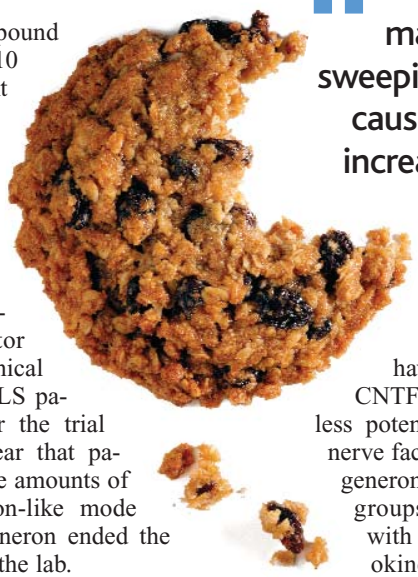
What does skin coloration have to do with erectile function—and can blocking melanocortin receptors reduce body weight? "It's an evolving story, and I don't think that it is completely understood at this point," says Dennis Earle, executive director of clinical and regulatory affairs at Palatin. What company researchers do know is that the pill increases blood flow to genitalia in both men and women, who are also involved in trials with the drug. And the pill, because it has a half-life of 2 hours and would be taken an estimated twice a week, would probably not affect long-term body weight or skin color, according to Earle. "The melanocortins are a very unusual system," says Alan Foster of Neurocrine Biosciences Inc. in San Diego, California, a system obesity drug researchers may have a tough time mastering. **–T.G.**

Interconnected. One oddball gene makes *agouti* mice (left) both fat and yellow, showing that the melanocortin system controls many physiological processes.

CREDIT: JANE SHIGI/VOLLUM INSTITUTE

Synthelabo in Paris have come up with an inhibitor of at least one cannabinoid receptor in the brain. These receptors support "the munchies," the food-craving effects of marijuana. The company is fairly close-lipped about their drug, called Rimonabant, and the status of ongoing clinical trials, but obesity researchers are eagerly anticipating word of their results.

The second compound is a molecule born 10 years ago as a treatment for amyotrophic lateral sclerosis (ALS). Researchers at Regeneron were investigating how a hormone called ciliary neurotrophic factor (CNTF) might keep motor neurons alive. The factor made its way into clinical trials in a group of ALS patients. But soon after the trial started, it became clear that patients were losing large amounts of weight in a starvation-like mode called cachexia. Regeneron ended the trial and went back to the lab.



> "We've got a major epidemic sweeping the world, causing a massive increase in death."
>
> –STEPHEN BLOOM

At about that time, Jeffrey Friedman's group at Rockefeller University in New York City announced the discovery of leptin; later, Louis Tartaglia's team at Millennium Pharmaceuticals in Cambridge, Massachusetts, found the hormone's receptor (*Science*, 7 February 1997, p. 751). These molecules signal to the body that fat stores are high and decrease appetite and metabolism.

"All sorts of bells and whistles started going off here," Yancopoulos recalls. The Regeneron team had just cloned and characterized the receptor for CNTF (*Science*, 3 March 1995, p. 1349). It turned out that the leptin and CNTF receptors look and act much alike: The two bear signature DNA sequences that are conserved in many species, and both receptors act upon the same neurons in an appetite-control center in the brain called the arcuate nucleus.

But there is a crucial difference. Leptin, when given to overweight people, doesn't seem to slim them down, as Amgen Inc. in Thousand Oaks, California, reported in 1999 after it conducted clinical trials of the hormone (*Science*, 29 October 1999, p. 881). Corpulent people already have high levels of leptin in their bloodstreams; they have become leptin-resistant, and injecting more of the hormone simply has no effect.

In contrast, CNTF doesn't seem to generate resistance. Yancopoulos's team showed that when normal mice are made tubby by being fed high-calorie diets and are then given CNTF, the animals lose an average of 35% of their body weight in 2 weeks. What's more, the animals don't seem to binge and regain weight later as do animals that are forced to diet. The same scenario appears to play out in humans.

Regeneron researchers have genetically modified CNTF to produce Axokine, a less potent version of the natural nerve factor. In phase II trials, Regeneron researchers injected five groups of 40 obese patients with different doses of Axokine or a placebo for 12 weeks. The best-responding group lost an average of 4.1% of their body weight (about 4.5 kg) compared to those given a placebo. And, according to Yancopoulos, who reported the team's results at an obesity meeting in New Orleans in April 2002, the Axokine-treated patients maintained their weight loss for up to a year after treatment began. Those in the control group, in contrast, gained weight. Phase III trials are now being conducted in 2000 obese people who will receive the drug for a year. If the results hold up, the weight loss would be "impressive" and "competitive [with], if not superior to," current treatments, Yancopoulos says.

But endocrinologists are expressing caution. Axokine appears to have long-term effects on the brain, some point out. How else would the drug block the usual yo-yo effects of dieting for at least 9 months after treatment?

Yancopoulos has another answer: Axokine, like leptin, works by activating a set of brain cells that produce appetite-dampening peptides, such as α-melanocyte-stimulating hormone (α-MSH), and blocking another set of neurons that produce appetite-stimulating molecules such as neuropeptide Y (NPY) and agouti-related peptide (AGRP) (*Science*, 10 March 2000, p. 1738). Chronic dieting does the opposite, leading to a voracious hunger that persists until such food-craving signals start to ebb—usually not until the body goes back to its previous weight.

Because CNTF lowers hunger signals from the start, people have "never dieted, as far as they know," says Yancopoulos. Indeed, volunteers taking the drug don't report that they are eating less, even though they are. The drug allows the body to establish a new, svelter set point, Yancopoulos suggests.

Leptin's partners in fat

Although leptin itself failed early weight-loss tests, obesity researchers are still doggedly pursuing its partners in fat. The hottest quarry is the melanocortins, a group of peptides and their receptors that execute leptin's food-suppression orders in the brain and body.

Gluttony. Successful antiobesity drugs will have to curb appetite even in times of plenty.

CREDITS: (TOP TO BOTTOM) PHOTODISC; FRANCIS G. MAYER/CORBIS

Two melanocortin receptors (MCR-3 and MCR-4) are headquartered in the arcuate nucleus. In response to leptin, the receptors dampen appetite. Pharmaceutical researchers are convinced that triggering them might bypass the cumbersome problem of leptin resistance.

Adding to the excitement, geneticists have discovered that some severely obese people bear mutations affecting various molecules of the melanocortin system, including the two receptors and their trigger, α-MSH. "We are hopeful about MCR-4 as a mechanism primarily because of the human mutant studies," says pharmacologist Alan Foster of Neurocrine Biosciences Inc. in San Diego, California.

The company has an MCR-4–targeted compound that appears to cause weight loss in rodents; researchers there expect to begin clinical trials in people next year. Other big pharma companies such as Merck and Chiron presented similar preclinical data at the 5th International Melanocortin Meeting in Sunriver, Oregon, in August. But most are working quietly, as the area is fiercely competitive.

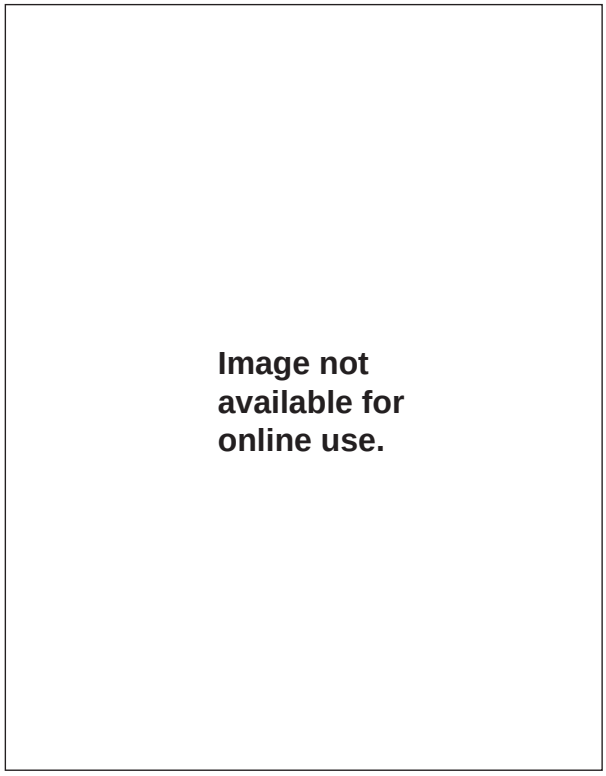
The melanocortin story also has a more potent twist. It comes from an offshoot of a drug targeted against MCR-1, which controls hair and skin pigmentation. Males taking the experimental drug to prevent skin damage from ultraviolet radiation got a surprise: erections. Now a small biotech is trying to exploit that side effect to come up with an alternative to Viagra (see sidebar on p. 850).

The yin and yang of eating

Beyond the leptin system and its role in long-term body fat regulation, another strategy has recently dazzled obesity researchers: targeting short-term food intake. Two peptides have emerged that control sensations of hunger and fullness. A hormone named ghrelin peaks before meals and triggers appetite, whereas a peptide dubbed PYY_{3-36} rises during meals and signals satiety. Researchers are trying out strategies to stifle the former and boost the latter in the hopes of controlling weight by limiting calorie intake.

Ghrelin was discovered in 1999 by Masayasu Kojima, Kenji Kanagawa, and colleagues at the National Cardiovascular Center Research Institute in Osaka, Japan, as a trigger for growth hormone receptors. The researchers were puzzled when the main site of ghrelin production turned out to be the gastrointestinal tract. After all, what does the stomach have to do with growth? Maybe little. Although ghrelin could target growth hormone–producing cells in the pituitary, the hormone also tickled another set of cells, located in the arcuate nucleus, that produce the appetite-stimulating neurotransmitters NPY and AGRP.

In 2000, investigators including Matthias Tschöp's team at Lilly Research Laboratories in Indianapolis, Indiana, infused the hormone, composed of 28 amino acids, into rodents and watched as the animals gained weight. The investigators also showed that ghrelin levels peak just before a meal. A year later, Kojima's group showed that ghrelin infusions hike up the firing rate in NPY/AGRP neurons. Antibodies that obstruct ghrelin hindered both neural firing and excess appetite. "Ghrelin is your gut's way of telling your brain when your stomach is empty and it's time to eat," says David Cummings of the University of Washington, Seattle.



No second helpings. A dose of peptide PYY_{3-36} makes volunteers eat less from a buffet.

If ghrelin turns out to be a governor of mealtime craving, then drugs that block the hormone might treat obesity by killing hunger pangs. But researchers first have to figure out whether braking short-term eating with a ghrelin inhibitor translates to breaking weight-gain patterns in obese people.

On the other side of the plate, PYY_{3-36} made its debut in August 2002 as a feeding squelcher. The molecule is a member of the NPY family, but it opposes NPY activity in the arcuate nucleus. Bloom's team at Imperial College reported that NPY and PYY_{3-36} compete for the same receptor in the hypothalamus, and in a complicated feedback loop, PYY_{3-36} thwarts the appetite-inducing effects of NPY.

Bloom has been testing infusions of PYY_{3-36}, at levels comparable to those after a meal, in both rodents and human volunteers. In the most promising results, six men and six women of normal weight received 90-minute infusions of the peptide. After a 120-minute rest period, the subjects chose freely from a buffet. Those who had received the hormone ate an average of one-third less than controls—but they did not report feeling hungrier, Bloom reported in the 8 August issue of *Nature*. The effect lasted for 12 hours, and volunteers did not appear to binge in the 24 hours afterward.

But giving plump people PYY_{3-36} or drugs that mimic its effects might not be enough to affect overall weight gain. "If you are going to target the arcuate nucleus, you have to hit multiple targets," Schwartz says. And those targets might have to include ghrelin, waiting perilously on the other side of the buffet table.

Another possible target is the product of a gene recently linked to stoutness by molecular geneticist Steven Stone's group at Myriad Pharmaceuticals in Salt Lake City, Utah. Using DNA samples from Utah families spanning multiple generations and a registry of more than 8000 patients with gastric bypasses, the Myriad group pinpointed the gene and published their results in April 2002. Stone is reticent to discuss details other than to say that the gene product is involved in "glucose metabolism trafficking."

So while obesity investigators continue their dogged search for pound-shaving drugs, the field is a mix of optimism and caution, for researchers have learned anti-obesity history's lessons. "We've got a major epidemic sweeping the world, causing a massive increase in death," Bloom says. "But I am sure that if we put more research into the system and give it another 10 years, there eventually will be an available tablet."

–TRISHA GURA

Trisha Gura is a Knight Science Journalism Fellow at MIT.