



SCIENTISTS HAVE FOUND A NEW WAY TO REV THE BODY'S METABOLISM: ACTIVATE ITS FAT CELLS.

release energy from food calories directly as heat. This spring, multiple studies in *The New England Journal of Medicine*—including one co-authored by Cypess, now a research associate at the Joslin Diabetes Center in Boston—confirmed that not only is brown fat common in adults, it's also important to metabolism: Younger, thinner people have more detectable brown fat than their older, pudgier counterparts.

As it turns out, doctors are still discovering how fat works. Rather than just a blubbery, lifeless mass, fat is now considered to be a sophisticated and scientifically complex biological organ, as important to the body as the liver or the kidneys. Scientists believe that fat secretes hormones and signaling molecules that coordinate behavior and health. White fat also plays a significant role in the immune system: A study published in August in the journal *Immunity* concluded that fat droplets help protect the body against immune-system invaders. A 2008 study published in *Cell Metabolism* found that the fat that accumulates around the thighs and hips, called subcutaneous fat, actually lowers risk of diabetes. “We were taught that white fat was something that stores energy very efficiently, and that’s it,” Cypess says. “Fat has undergone a renaissance.”

Despite this new perspective, doctors agree that most people have a lot more white fat than they need. A whopping 34 percent of Americans over the age of 20 are obese, and much of the fat that accumulates on an obese body is visceral:

THE FUTURE OF FAT

> BY MELINDA WENNER
> ILLUSTRATION BY YUKO SHIMIZU

Five years ago this February, Aaron Cypess had an epiphany about fat. A fellow in endocrinology at Boston's Beth Israel Deaconess Medical Center, Cypess happened to be attending a lecture in which a doctor presented images of human PET scans. At one point, Cypess recalls, the doctor indicated an area corresponding to the neck and said, rather dismissively, “Oh, that’s brown fat.” Cypess was taken aback. After the lecture, he approached the doctor and told him he must have been mistaken: Everyone knows there’s no brown fat in human adults. The doctor responded, “Yeah, there is. We see it all the time.” Cypess paused. “Wait a minute,” he said. “Really?”

Brown fat has long been known to exist in infants and animals such as mice, but until recently scientists thought it disappeared before human adulthood, leaving only the white fat that’s associated with weight gain. Unlike white fat, which stores energy, chestnut-colored brown fat burns it. Brown fat cells contain a large supply of organelles called mitochondria, and an enzyme that allows them to

It surrounds vital organs and increases the risk of diabetes, as well as cancer and stroke. For these people, the discovery of brown fat, which is concentrated in the neck and chest, provides a glimmer of hope. Scientists have now begun to think about fat as a potential treatment for conditions such as obesity, rather than just a cause.

FLIPPING THE FAT SWITCH

→ **Cypess's research** has shown that, besides young, thin people, women are twice as likely as men to have significant amounts of active brown fat—perhaps because with less muscle mass, they need brown fat to stay warm. In fact, temperature seems to be an important controller of brown fat activity. A team led by Sven Enerbäck, a medical geneticist at the University of Gothenburg in Sweden, found that when subjects spent 2 hours in a cold room wearing thin clothing and intermittently soaking their feet in ice water, their brown fat burned 15 times more energy than it did at room temperature. One subject had enough brown fat to lose 8 to 9 pounds per year. Dutch researchers found active brown fat in 23 out of 24 subjects when they were cold, but not when they were warm. And research at the University of Nottingham in England revealed brown fat activity was closely associated with seasonal decreases in daylight as well.

Animal studies also suggest brown fat boosts weight loss. Last year, Stockholm University scientists found that mice that could not make brown fat gained weight 50 percent faster than mice that could. In a 2008 study, mice fed a high-fat diet and kept at room temperature ended up nearly four times heavier than mice fed the same diet and housed at 39 F. Researchers estimate that just 2 ounces of active brown fat could burn 300 to 500 calories a day. “You don’t need much to

have a profound effect on your body’s metabolism,” Cypess says.

So how do you turn brown fat on without having to soak your feet in ice water? As a postdoctoral fellow at the Harvard-affiliated Dana-Farber Cancer Institute in Boston, Patrick Seale identified a protein called PRDM-16 that is present in every brown fat cell but absent from white fat cells. When he turned off PRDM-16 activity in young brown fat cells, they changed into muscle cells. Now an assistant professor at the University of Pennsylvania School of Medicine, Seale is working on identifying genes that may turn PRDM-16 on.

Seale’s adviser at Dana-Farber, Bruce Spiegelman, is testing a therapy that involves removing white fat precursor cells from animals, inserting active PRDM-16 and then transplanting the cells back into the animals to see if they lose weight. Mitchell Lazar, director of the Institute for Diabetes, Obesity and Metabolism at the Univer-

Ultimately, what Seale and Cypess envision is a “brown fat pill”—a drug that boosts the activity of brown fat through molecular means. “I have patients who are 400 pounds,” Cypess says. “I have to find a way to help them out.” Of course, they realize such a drug won’t provide a quick fix for obesity. But brown fat could help people achieve weight loss goals by burning, say, an extra 500 calories a day.

Until a pill becomes available, there are ways for people to rev up their brown fat activity. “I don’t think you could get a lot of people to put up with [cold] therapy,” Enerbäck says, but it could help to turn down your home’s central heating and to spend some time outside in the fall and winter. Studies suggest that people who work outdoors have higher brown fat activity than average, so it’s not absurd to think that walking to work on a brisk day could boost your metabolism.

As scientists continue to study fat in a new light—as an important organ

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sity of Pennsylvania School of Medicine, admits that the idea seems pretty farfetched. “On the other hand, I can’t really think of any reason why it wouldn’t work,” he says.

CREATING A MAGIC PILL

→ **Cypess and his colleagues** are focusing on different proteins, including one called BMP-7 that aids bone growth. (Bone communicates regularly with fat.) Recently, one researcher found that BMP-7 increases the production of brown fat and protects against obesity in mice. The U.S. Food and Drug Administration has already approved a BMP-7 drug for use in spinal surgery, so Cypess is testing the drug’s effects on surgical patients to see if it boosts brown fat too. “If it works, we’ve leapfrogged past several years of research,” he says.

in the body’s endocrine system—they are bound to find more opportunities. For example, a study published in July by Paul MacLean and his colleagues at the University of Colorado at Denver revealed new insight into exercise and weight loss: Physical activity reduces weight by increasing the brain’s sensitivity to appetite-suppressing hormones like leptin and insulin more so than by burning calories. According to MacLean, it may make the brain “more receptive to what the leptin and insulin are trying to say.”

Perhaps, then, it’s possible to conceive of an “exercise pill” too. Sure, it sounds ridiculous. But given the gravity of the situation, there may not be any harm in being imaginative. “We certainly need creative new ways of thinking about combating the obesity epidemic,” Enerbäck says. **PM**

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