

# Albert Lasker Basic Medical Research Award

## Award Description

### **Douglas Coleman and Jeffrey M. Friedman**

*For the discovery of leptin, a hormone that regulates appetite and body weight—a breakthrough that opened obesity research to molecular exploration.*

The 2010 Albert Lasker Basic Medical Research Award honors two scientists for their discovery of leptin, a hormone that regulates appetite and body weight. **Douglas Coleman** (Jackson Laboratory) established that an appetite-suppressing substance circulates in the bloodstream and signals a second molecule to curb hunger. **Jeffrey M. Friedman** (Rockefeller University) isolated the gene that encodes the appetite suppressant and showed that fat cells release it. Their studies and subsequent findings demonstrated that this chemical, leptin, plays the central role in a self-regulating circuit: As fat accumulates, it exudes leptin, which binds to a receptor in the brain that quells the desire to eat. Coleman and Friedman have launched new understandings of obesity and disorders that result from perturbed leptin activity. They have overturned conventional notions with the insight that many overweight people suffer not from lack of willpower, but from metabolic disruptions.

Individual humans eat approximately a million calories per year, yet most people's weight remains stable over long periods. By the 1950s, scientists were devising schemes for how the body balances food intake with energy expenditure. In 1953, Gordon C. Kennedy (National Institute for Medical Research, London) suggested that some compound, whose quantity mirrors that of stored fat, acts on the brain's hypothalamus, a site that was known to house appetite centers. In the late 1950s, Romaine Hervey (University of Cambridge) created lesions in the hypothalamus that subsequently caused rats to eat voraciously. He then surgically connected pairs of animals—one with hypothalamic damage and one with an untouched brain—such that elements of their circulatory systems mixed. The normal rats stopped eating, Hervey reported. He proposed that chemical information from an overfed body travels through the bloodstream to intact appetite centers, which respond by subduing hunger in the normal animals.

Components of a feedback system that depends on a blood-borne molecule had therefore surfaced by the end of the 1950s. However, the signal and its hypothalamic target eluded identification. Without that information, no one could submit the ideas to experimental scrutiny or define the mechanism by which the hypothetical substance operates.

### **Weighty connections**

In 1965, Coleman began studying a mouse strain that had emerged at the Jackson Laboratory. Disturbances in its metabolism resembled those that occur in human diabetes, and one of its most striking characteristics was obesity. This mouse owed its troubles to two defective copies of a gene that researchers dubbed *diabetes (db)*.

Coleman wondered whether something in the mutant mice might trigger problems in normal mice or, conversely, whether something in normal mice might cure the "diabetes" animals. He tested these ideas through an experimental approach similar to Hervey's, in which scientists sew together two animals so that blood-borne factors can move from one individual to the other. If the sick mice harbored a harmful substance, it would enter the normal animals' bodies and spur weight gain, Coleman reasoned. If the normal animals carried a health-promoting material, it would ease the sick animals' symptoms.

The outcome proved more interesting than either of those possibilities, Coleman reported in 1969. Rather than gorging, as the "diabetes" mice did, the normal mice stopped eating and died, apparently from starvation. The "diabetes" mice must have released a factor that quashed the normal animals' drive to eat, Coleman surmised—a factor to which mutant animals could not respond.

To investigate further, he turned to another overweight mouse, this one called "obese," whose aberrant physiology arises from two defective copies of a different gene (*ob*). Although the "obese" and "diabetes" mice displayed almost identical features—heft and other metabolic irregularities—they behaved radically differently after Coleman connected their circulatory systems. Nothing happened to the "diabetes" animals, but the "obese" mice starved to death, just as the normal rodents had in the previous experiment. In contrast, attaching normal mice to "obese" animals did not perturb the normal creatures and caused the "obese" ones to trim food consumption and gain less weight than usual.

Together, these results implied that normal mice make a substance that restrains appetite, but not to a dangerous degree. In contrast, "obese" mice do not manufacture an operational satiety factor, but they can detect and react to it. "Diabetes" mice overproduce the substance, thus causing normal and "obese" mice to stop eating—but they fail to respond to it. To validate these ideas, scientists needed to identify the *db* and *ob* genes and protein products, a task that posed insurmountable challenges at the time.

### **Hungry for genes**

As a postdoctoral fellow, Jeffrey Friedman was captivated by how molecules control complex behaviors. His work led him to the "obese" mice and, by 1986, when he joined the faculty of Rockefeller University, he had decided to track down the *ob* gene. Researchers had just developed methods that allow scientists to isolate genes based on their location in the genome. Despite the technological power of this approach, the undertaking was enormously ambitious. Previous work had established that the *ob* gene resides within a large stretch of mouse chromosome 6, so Friedman, in collaboration with Rudolph Leibel (Rockefeller University), first narrowed its position to a much smaller region. Then Friedman and his lab members analyzed hundreds of molecular markers in almost 1000 mice to home in on it.

In 1994, Friedman's team reported that it had isolated and sequenced the *ob* gene. The researchers then confirmed its identity by analyzing two strains of *obese* mice: One failed to manufacture *ob* messenger RNA, whereas the other overproduced a version of it that was predicted to encode a nonfunctional protein.

Normal animals displayed *ob* gene activity in fat, but not in other types of tissue, Friedman found, and he isolated the human version of the *ob* gene from fat cells. These observations were intriguing, given Kennedy's proposal four decades earlier and the dogma that fat passively stores energy.

To explore the idea that fat produces an *ob*-encoded protein, which functions as a hormone, traveling elsewhere in the body to govern appetite, Friedman—and soon others—tested several predictions. First, the molecule should appear in the circulation. In 1995, Friedman's group engineered bacteria to fabricate the protein (OB), generated antibodies that bind to it, and showed that all mammals tested, including humans and rodents, carry OB in their blood. Furthermore, "diabetes" mice make excess quantities of it, as predicted from Coleman's experiments, and its amounts decrease in normal animals and obese humans after weight loss.

The model also implies that OB administration curtails food intake and body weight in "obese" and normal mice, but not in "diabetes" animals; Friedman and others confirmed this prediction. Furthermore, the protein exerts particularly potent effects when injected into the cerebrospinal fluid, suggesting that it acts directly on the brain. Because the *ob*-encoded protein makes animals slim down, Friedman named it leptin, from leptos, the greek word for "thin."

In late 1995, a group led by Louis A. Tartaglia (Millennium Pharmaceutical Incorporated, Cambridge, MA) identified a gene whose protein product binds leptin. Two months later, Friedman and Tartaglia independently showed that this leptin receptor is encoded by the *diabetes* gene and has multiple forms, one of which is defective in "diabetes" mice. Subsequent gene-activity studies from Friedman's lab implied that the normal version of this receptor variant is especially abundant in the hypothalamus.

Together these results explained Coleman's findings. Because the "diabetes" mice lack the receptor that senses the satiety factor, now known as leptin, hunger persists regardless how much food the animals consume. As they gain weight, the accumulating fat produces more and more leptin, which directs normal and "obese" mice to stop eating. "Obese" animals do not make functional leptin, but they respond to it when they receive it from "diabetes" or normal mice.

### Fat chances

Friedman's discoveries fueled intense efforts to uncover the mechanism by which leptin exerts its effects and apply these findings to clinical challenges. In 1997, Sadaf Farooqi and Stephen O'Rahilly (Addenbrooke's Hospital, Cambridge) identified rare people with mutations in its gene and showed that they are extremely sensitive to leptin-replacement therapy (see photograph). Most obese individuals, however, possess large amounts of circulating leptin, yet remain overweight. Researchers are trying to understand why ordinary obese humans resist their own leptin and are strategizing how to counteract this situation.



**Enlightened treatment.** Daily injections of leptin dramatically reduced appetite and weight in a child with leptin deficiency. At three years old (left), this boy was morbidly obese; at seven years old (right), he was in the 75th percentile for weight. (Courtesy of Stephen O'Rahilly and Sadaf Farooqi, with permission of the child's parents.)

Scientists have also discovered that inadequate leptin underlies other pathologies. In lipodystrophy, for example, patients lack sufficient fat tissue and underproduce leptin; symptoms include insulin resistance and high cholesterol levels. Although inherited lipodystrophy is uncommon, a significant proportion of people with HIV acquire the condition. Preliminary studies suggest that leptin therapy can provide therapeutic benefits for these individuals. This treatment can also restore menstrual cycles that have stopped in women who subject

themselves to extreme exercise regimes or reduced food intake.

Coleman and Friedman have fostered an explosion in our knowledge about how the body manages hunger and weight control. Leptin presides over a network that plays a crucial role in normal physiology and disease, and scientists have only begun to explore the myriad ways that we might manipulate this system to enhance people's health and well being.

By Evelyn Strauss