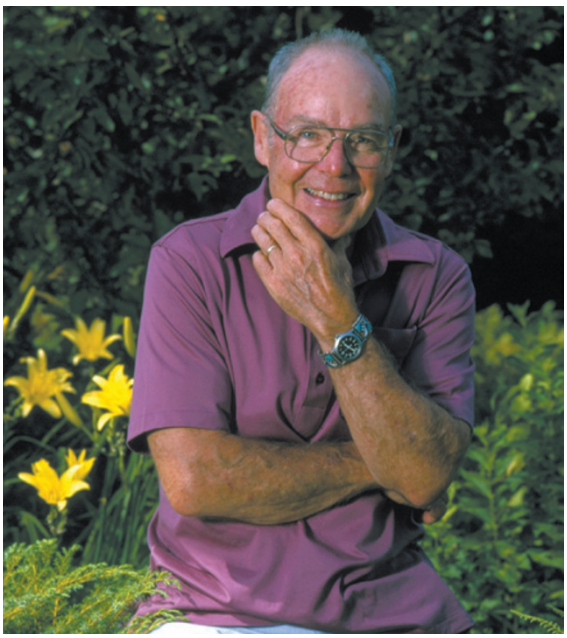
Douglas Coleman

(1931–2014)

Biochemist who revealed biology behind obesity.



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More than 40 years ago, when few thought that obesity needed an explanation beyond a lapse in willpower, Douglas Coleman proposed that body weight and appetite are regulated by a then-undiscovered hormonal system.

Coleman was born in Stratford, Canada, in 1931, as the challenges of the Great Depression were reverberating around the world. When he was young, his parents lost their jobs in furniture manufacturing. The extended family lived together in one house, surviving by hunting for rabbits and squirrels and by farming in their backyard. As circumstances improved, his father opened a business repairing radios and refrigerators. Rather than joining him, Coleman went to study chemistry at McMaster University in Hamilton, Canada. There, he met a fellow chemistry student, Beverly Benallick. They married and shared a life together for the next 50 years.

After receiving a PhD in biochemistry from the University of Wisconsin in Madison, Coleman was recruited to the Jackson Laboratory in Bar Harbor, Maine. There, he studied two stocks of mutant mice. Both carried recessive mutations that produce marked obesity. The *ob* stock was severely obese and mildly diabetic, whereas the *db* stock was less obese and severely diabetic. Coleman and his colleagues used cross-breeding to study both mutations in the same inbred strain, and revealed that the strain differences vanished when either mutation was carried on an identical genetic background. In a series of important papers, Coleman showed that neither gene acts alone, but is modified by others.

When mutations in different genes produce the same effect, they often function in the same pathway, and Coleman began to probe how the genes work together. With developmental geneticist Elizabeth Russell and others, he launched in the 1960s a now-iconic set of experiments, in which he stitched together the skin and muscle of living mice of the different strains so that they shared a circulatory system. The *ob* mice that were surgically joined to normal or *db* mice ate less and lost weight, so Coleman concluded that *ob* mice lacked a circulating factor (provided by the conjoined partner) that suppressed food intake and body weight. Similarly, normal mice paired with *db* mice starved to death. Coleman suggested that *db* mice lacked a receptor to detect the weight-suppressing factor and so overexpressed it, producing levels so high that conjoined mice sensitive to the factor stopped eating.

Coleman spent years pursuing his hypothesis. Although he was not able to isolate the 'satiety factor' from circulating blood, his confidence in his conclusions never wavered; he explained that he had spent years trying to disprove his hypothesis and was never able to do so.

It took more than two decades for Coleman to be proved correct. Inspired by his experiments, my laboratory at Rockefeller University in New York City cloned the *ob* gene in 1994 and identified leptin, a hormone secreted by fat that regulates food intake by binding to its receptor. The leptin receptor is encoded by the *db* gene and expressed in the hypothalamus, a region of the brain known to control basic functions. Coleman also lived to see the US Food and Drug Administration approve the hormone as a treatment for severe diabetes associated with lipodystrophy, an often devastating disease resulting from an absence of fat tissue.

The discovery of leptin has led to the elucidation of a robust system that maintains relatively constant levels of fat stores. When fat mass falls, so too do leptin levels in the blood, stimulating appetite and suppressing energy expenditure. When fat mass increases, leptin levels rise, suppressing appetite. These findings have transformed obesity research, overhauling the scientific view of fat cells from passive storage vats into dynamic regulators of metabolism.

Coleman arrived at work by 7 a.m. each morning and was sure to be home by 5.30 p.m. for family dinner. He was a keen hiker and sailor, and hunted for birds with a series of Brittany spaniels. Coleman was happiest working alone, assisted by two technicians at most. Over time, he concluded that his solitary style of research had become archaic. Satisfied with his achievements, he retired at age 62 rather than trying to reinvent his laboratory.

Coleman spent the following decade travelling the world with Beverly, always returning to their house by the sea in rural Maine. They were deeply committed to protecting lands and forests. He bequeathed their 20-hectare woodland and most of his assets to promote conservation.

Coleman felt that he had a great life despite, in his words, having endured two terrible tragedies: the loss of his 11-year-old son John to bone cancer and of Beverly to Alzheimer's disease in 2006. Tellingly, he did not list as a tragedy his own battle with an aggressive carcinoma of the face. Stoking his wood stove each morning, he found things to look forward to despite constant pain and eventual blindness. He also enjoyed the long-delayed recognition he so richly deserved, travelling the world with his sons and friends to receive awards.

Coleman walked with a brisk gait that gave the impression that he was headed somewhere. He spoke the same way, always amiably, but with purpose. When he did something, he did it meticulously and with conviction. Content to go where the data led him, he followed a path that helped to illuminate the molecular machinery that underlies a major issue in public health. ■

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