



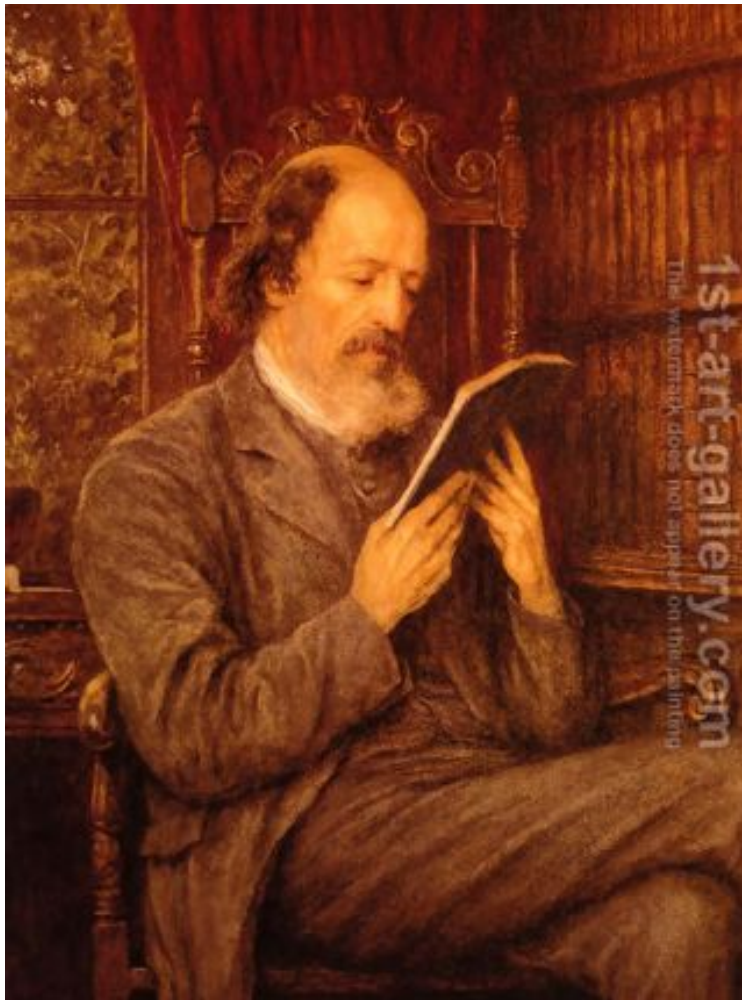
**Sylvia R. Karasu M.D.**  
The Gravity of Weight

# A Point of Reference: Weight and the Concept of Set Point

Is the set point just another point of no return for weight-challenged people?

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Poet Laureate Alfred, Lord Tennyson, author of "Locksley Hall"

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In his less well-known poem of an imaginary childhood place *Locksley Hall* (1842), Alfred, Lord Tennyson, the famous Poet Laureate of England, writes "Science moves, but slowly, slowly, creeping on from point to point." There are many points in science—including points of divergence and convergence, points of reflection and refraction, and point mutations among others, but the point most closely associated with weight is the set point. Is the set point a viable concept or merely one of Tennyson's "fairy tales of science?" Most people have heard of this concept but few may really understand what researchers have in mind by it.

The concept of a set point for weight, i.e., an internal physiologically regulated system, though, was defined in series of papers by Dr. Richard E. Keesey and his colleagues in the 1970s and 1980s. Originally taken from an engineering model, it was seen as a homeostatic feedback control system (Mrosovsky and Powley, *Behavioral Biology*, 1977) and as analogous to a set point for body temperature or even blood pressure—though

there is considerably more variability for weight among people than for blood pressure or body temperature. It grew out of the observation that remarkably our weight remains within a fairly constant range despite major fluctuations in our activity levels as well as in the varieties and quantities of food our bodies process both in the day-to-day short-term and long-term. For example, Jules Hirsch, (2003, *Dana Foundation lecture*), one of the early pioneers in obesity research at Rockefeller University, once observed that during our lifetime, our bodies process about 70 million calories or approximately 14 tons of food.



Set point regulation is analogous to blood pressure and temperature regulation by our body

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Speculation about a control mechanism that regulated the amount of fat in the body, though, began to occur in the 1950s. For example, GC Kennedy (*Proceedings of the Royal Society of London, Biological Sciences*, 1953), working with rats, suggested that fat itself might send a signal to the brain to regulate the amount of fat in our bodies. It would not be until the 1970s, though, that leptin, the hormone produced by adipose tissue, was isolated in the Rockefeller University labs of Jeffrey Friedman and “provided strong molecular evidence for such a feedback system.” (Speakman et al, 2011, *Disease Models and Mechanisms*)

Other evidence for a set point grew out of human data that when people gain or lose weight (i.e. “the system is perturbed”), the body seems “to defend” the original weight. That is why after a weight loss, there is a tendency for many people to regain the lost weight. (Speakman et al, 2011) There is, though, an “asymmetry” in this process—namely that the body seems to defend against weight loss far more effectively than against weight gain, probably as an evolutionary advantage when food cycles were more variable. No one, though, has actually located the elusive set point or whether it

is even one area, though there has been past simplistic speculation that it is in the hypothalamus.

Maclean and colleagues (2004, 2006), writing in the *American Journal Physiology: Regulatory, Integrated and Comparative Physiology*, studied



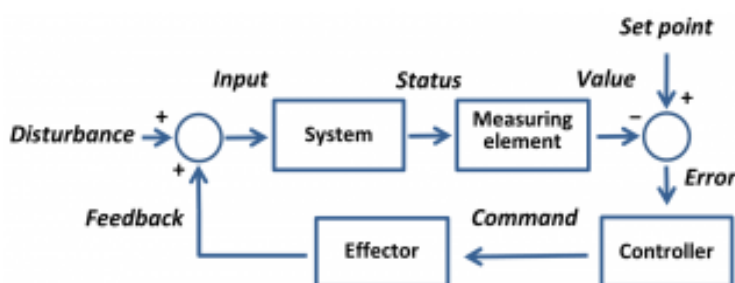
Early theories suggested the set point was located in the hypothalamus; it is more likely it is not localized to one area

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obesity-prone rats and noted metabolic factors in rats are easier to study because there are not contaminating human motivational factors (e.g. peer pressure to be thin; wishes for an ideal physique). These researchers found there was a “metabolic propensity” for their rats to regain weight after a period of caloric restriction and subsequent weight loss, both by an increased appetite and a decrease in resting metabolic rate. But MacLean et al noted that studies with humans can be inconsistent and found it “reassuring” that humans are able to counteract any metabolic tendency to gain weight by changing their behavior (e.g. consciously exercising, eating less, even taking medications for weight loss.) Levin (2004, writing in the same journal) summarized the controversy by noting that the regulation of fat accumulation in humans is very complicated and determined by “genetic, gender, perinatal, developmental, dietary, environmental, neural, and psychosocial factors.”

William Bennett (*New England Journal of Medicine, Editorial*, 1995) noted that the set point seems to respond slowly “rather than rapidly to

deviations from the internal ideal” and involves both eating and physical activity. Bennett clarified that although these two behaviors are thought to be “largely voluntary...there can be considerable ambiguity about the degree of volition” involved in either activity and “such behavior assumes a certain biologic inevitability.”



The set point concept came from an engineering model of feedback control

Source: set point control; Brews ohare, Public Domain, Creative Commons, Wikimedia Commons.org

The set point model has limitations. It does not explain why our set point is somewhat adjustable —i.e., why most people do gain some weight throughout their lives, particularly under certain environmental conditions, such as changes in marital status, age, social class, or even if they are “couch potatoes.” In other words, though the set point theory is “rooted in physiology, genetics, and

molecular biology,” and “postulates an active feedback mechanism linking adipose tissue (stored energy) to intake and expenditure,” it does not sufficiently explain the contribution of the so-called “obesogenic environment” and social issues that contribute to weight gain. (Speakman et al, 2011)

There is another model, the *settling point model*, that proposes a passive (rather than active regulation) feedback system in which weight can “drift” (Farias et al, *Metabolic Syndrome and Related Disorders*, 2011.) This model does focus on environmental and social issues, but it does not, however, sufficiently focus on the more genetic and biological issues and hence the two models create an “artificial” divide between genetics and the environment. (Speakman et al, 2011) Another proposed model, the *general intake model*, emphasizes that there are “compensated factors” (e.g. primarily physiological) and “uncompensated factors” (primarily environmental) that impact weight regulation and can vary considerably from person to person, but it does not assume there is a set point. A fourth model is the *dual intervention point model*—a “more realistic version of the set point model” (Speakman et al, 2011) that can incorporate both genetic and environmental contributions in which there are upper and lower limits where “physiological regulation of weight/ and or fat” becomes active.

Bottom Line: In *Locksley Hall*, Tennyson wrote “Knowledge comes, but wisdom lingers.” Whether we find the anatomical place or places for a set point remains to be seen. For many researchers, the concept of set point is too simplistic to explain the complexities and daunting science of weight control. For some people, though, a functioning set point becomes a kind of an anchoring point of reference for their weight; for those less fortunate, whose weight continues to climb and whose set point seems dysfunctional, it may be a point of no return.

Note: I could not find many papers in very recent years on set point but the term continues to appear in the literature. For one paper, see Ravussin et al, *Molecular Metabolism* (2014), on rats given leptin exogenously and the relationship to set point.





Alfred, Lord Tennyson was buried in Westminster Abbey, in the Poets' Corner

Source: Westminster Abbey, Public Domain, Wikimedia Commons.org

## About the Author



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**In Print:** *The Gravity of Weight: A Clinical Guide to Weight Loss and Maintenance*

**Online:** my own website

