The drive to regain is mainly in the brain

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The extremely high rate of recidivism in the treatment of human obesity is a well-documented phenomenon (18, 19, 57). The factors that underlie this high failure rate are widely debated, and no consensus has yet been reached. One seemingly insurmountable problem in identifying potential etiologic factors is that such studies become hopelessly mired in the interaction between homeostatic (metabolic) and nonhomeostatic (reward) controls of food intake in humans. For that reason, animal models have provided important new insights into the way in which mammals balance their intake and output of energy under tightly controlled conditions. In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, MacLean et al. (39) present a superbly constructed and beautifully interpreted set of studies on the behavioral and metabolic responses during the development of obesity, chronic food restriction, and relapse after ad libitum access to food. To do this, they assessed energy intake and expenditure in obese rats for up to 16 weeks of restricted feeding (“weight-reduced”) followed by 8 additional weeks of refeeding (“relapsed-obese”). Given the average life span of rats (~2 yr) vs. humans (~70 yr), this experiment is comparable to observing reduced obese humans for more than 10 years under strictly controlled conditions. The depressing conclusion is that weight-reduced obese rats had a persistent decrease in their resting energy expenditure and increase in their metabolic efficiency that did not attenuate with continued restriction. Furthermore, when external constraints on food intake were removed, chronically restricted rats inexorably regained lost weight almost exactly back to the level they would have maintained if never restricted. They did this initially by increasing food intake while maintaining their lowered metabolic rate. As refeeding rats regained their projected unrestricted body weights (adipose stores), their rate of intake decreased and their metabolic rate normalized. Because similar responses appear to occur in humans (20, 56), the extrapolated message for obese humans seeking long-term weight loss is to find some way to increase your metabolic rate and control your hunger for life!

The MacLean et al. study (39) tells us what happens but not why it happens. What and where is the internal set point that leads animals and humans to doggedly return to their previous body weights when they are either over- or underfed for prolonged periods? Clearly, there is no one set point localized in one precise place. The defended body weight and adipose mass can be manipulated by changing dietary content and palatability (27), as well as by conditions that change neural function and the metabolic and hormonal state of the individual (13, 16, 25, 30, 37, 41, 42, 53). In fact, energy homeostasis is controlled by a continuous dialogue between the periphery and brain. Genetic, environmental, and psychosocial inputs are superimposed on this dialogue. The summated inputs are integrated within metabolic sensors in the periphery and brain and lead to changes in the regulated adipose mass (39, 40). Leptin and to a lesser extent insulin are the two currently known hormonal signals that tell the brain how much fat is stored in peripheral depots (60). These hormones converge on select brain areas that contain specialized “metabolic sensing” neurons (33). Such neurons have leptin and insulin receptors but also utilize glucose and other metabolic signals from the periphery as signaling molecules to control the rate of neuronal activity. These neurons summate both tonic and phasic hormonal, metabolic, and other hard-wired neural signals from the periphery and surrounding brain areas to alter membrane potential, firing rate, transmitter release, and gene transcription (33). The integrated outputs from these metabolic sensing neurons is passed on to neuroendocrine and behavioral effector systems involved in the control of energy homeostasis (33).

This homeostatic feedback system seems primarily designed to ensure that individuals will consume and store sufficient food during periods of surfeit to allow them to survive times when fuel availability is limited. This suggests that survival is more dependent on the adequate functioning of anabolic than catabolic systems. During prolonged food restriction, adipose-derived leptin and adiposity-associated insulin levels fall. Leptin and insulin both exert inhibitory feedback on anabolic hypothalamic peptides like neuropeptide Y (NPY) and positive feedback on catabolic peptides like proopiomelanocortin (POMC), the precursor of the melanocortin-3/4 receptor agonist α-melanocyte-stimulating hormone (25, 30, 52, 60). Central injections of NPY increase food intake and reduce energy expenditure and fat oxidation (2, 3), and melanocortin agonists have the opposite effect (4). When leptin or insulin levels decline during food restriction or when their central signaling is genetically disrupted, NPY expression increases and POMC expression decreases, and animals enter an anabolic state (17, 51, 52, 55, 58, 60). Thus the increased metabolic efficiency of food-restricted rats and their increased food intake and metabolic efficiency during relapse, as demonstrated by MacLean et al. (39, 40) and others (1, 5, 20, 26), are exactly what would be predicted from an examination of their hypothalamic NPY and POMC expression. Furthermore, replacement of either leptin or insulin acts to normalize both the anabolic tilt of central regulatory peptides and the peripheral metabolic rate even if fat stores are not restored (48, 49, 51). While vastly oversimplified with regard to the myriad other peripheral and central regulatory systems involved in this process, the general message is the same: anything that reduces the adipose mass or interferes with central leptin or insulin signaling leads to a net central and peripheral anabolic tone and fosters the development of obesity.

The hypothetical set point for the level at which adiposity is regulated is determined by genetic, gender, perinatal, develop-
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mental, dietary, environmental, neural, and psychosocial factors. In some rodents, there appears to be a genetically determined level at which they regulate their adipose stores when provided with adequate dietary fat. The evidence for this comes from the study of obesity-prone rats. Such rats have a number of abnormalities of neural function when kept at a relatively low level of adiposity by intake of low-fat diets (8, 9, 11, 21–24, 29, 31, 32, 35). Unlike obesity-resistant rats that quickly reduce their intake of a high-fat diet to compensate for the increased caloric density, obesity-prone rats remain hyperphagic for weeks despite early increases in plasma leptin and insulin levels that should normally reduce intake (32). Their caloric intake is reduced when leptin levels exceed what appears to be an elevated central threshold for sensing leptin (21, 29, 31). In fact, obesity-prone rats on low-fat diets appear to be so far below their preprogrammed set point that as little as 1–2 wk of high-fat diet exposure permanently raises their defended body weight (29). Obesity-resistant rats, on the other hand, maintain the same lower level of defended adiposity regardless of the fat content and caloric density of their diet (29, 32). Once obesity-prone rats reach a higher level of adiposity, many of their previous abnormalities of neural function are corrected, and they avidly defend this higher level against chronic caloric restriction (8, 9, 11, 21–24, 29, 31, 32, 35, 38, 59). In their elegant paper, MacLean et al. (39) have demonstrated the way in which metabolic and behavioral responses are modified to defend such a raised set point. The permanence of this upward resetting of the defended adipose mass may occur in peripheral tissues but has all of the external hallmarks of long-term neural plasticity. Although evidence that such plasticity occurs has never been conclusively demonstrated, there are irreversible, genotype-specific changes in transmitter receptor function that occur in adult obesity-prone and -resistant rats subjected to chronic changes in dietary content (22, 36). In addition, the maternal environment can have a major impact on neural programming (6, 14, 15, 28, 34, 43–47). The bad news is that maternal obesity during pregnancy can increase the likelihood that offspring will alter their neural development in such a way as to promote increased obesity and insulin resistance (28, 34). At least in rats, this effect occurs only in offspring of mothers with an obesity-prone genotype (28, 34).

Thus there appears to be a powerful genetic program that drives obesity-prone individuals to gain weight when provided with unlimited supplies of high caloric density food. Add to that the potent obesogenic effect of highly palatable foods available in our society, and you have a recipe for an obesity epidemic. Intake of such foods is largely regulated by homeostatic reward systems that override the usual constraints provided by homeostatic feedback systems. MacLean et al. (39) have shown how powerful and reproducible the drive to regain lost fat stores remains, despite the human equivalent of years of restricted intake. The major question posed by such studies is how we can overcome this system, which is apparently designed to preserve the status quo with regard to body weight and adiposity. One strategy would be to replace leptin to inhibit the anabolic shift of central regulatory pathways and the increased metabolic efficiency that occur when leptin levels fall with chronic weight loss (48). This could potentially avoid the problem of central leptin resistance that occurs in obese individuals (10, 48, 50, 54). Another strategy is to use physical exercise to increase energy expenditure during caloric restriction (12). Anecdotal reports from “successful” weight-reduced obese subjects support an important role for exercise in maintaining a lower adipose mass in some individuals (61, 62). In rats, chronic exercise not only lowers the defended adipose mass but also pushes the central neuropeptides involved in energy homeostasis back toward an equal anabolic and catabolic balance (25). Exercising rats lose adipose mass but do not show the increased anabolic neuropeptide tone seen in rats that are food restricted to achieve the same reduced level of adiposity. Importantly, exercising rats do not increase their energy intake to compensate for their lost adiposity, despite appropriate lowering of leptin levels. Another weight loss strategy is the use of pharmacological agents to lower the defended set point. Drugs like fenfluramine (53) and sibutramine (30) may do exactly that. In the case of sibutramine, chronic administration lowers the defended adipose mass, apparently by preventing the usual drive toward an anabolic balance among brain neuropeptide systems that is normally associated with such adipose loss (30).

Of course there are obvious problems and potential limits to each of these strategies. It is likely that chronic administration of leptin at levels sufficient to nullify the reduced metabolic rate of weight-reduced obese humans will eventually reproduce the same leptin resistance they had when obese. Exercise, while it appears to prevent compensatory increases in homeostatic eating in obese rats, has still not proven adequate to dampen the incredibly strong nonhomeostatic forces to eat and regain lost weight to which obese humans are exposed in our society (56, 57). Also, it requires enormous willpower to maintain the high levels of exercise needed to sustain a permanently lowered level of adipose stores. Finally, there are obvious limitations to the pharmacological treatment of obesity. First, the results of MacLean et al. (39) support the contention that weight-reduced individuals, like hypertensives and diabetics, are likely to require life-long therapy. There are no currently available drugs that meet the minimal criteria of being safe, acceptable, and effective for such long-term treatment. When such drugs are eventually made available, it is likely that there will be a limit to the amount of weight loss an individual drug can produce. Thus multidrug therapy, with agents acting on different central and peripheral targets, will probably be required to sustain effective, continued weight loss in most obese individuals. MacLean et al. (39) have shown how potent the metabolic drive is to regain lost weight in obese individuals. This drive alone is probably sufficient to explain the incredibly high recidivism rate in the treatment of obesity. For now, we are left with the therapeutic strategy of advising lifestyle changes in diet and physical activity. Short of surgical restructuring of the gastrointestinal tract, it is unlikely that we will be very successful in helping a large number of obese individuals to exert sufficient willpower to override the powerful forces designed to drive them back to their obese set points. Thus it is this observer’s bias, strongly reinforced by the studies of MacLean et al. (39) and others (7), that it will require life-long pharmacological treatment to help most obese individuals make the necessary lifestyle changes required to effectively maintain a safe weight-reduced level of adiposity.
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