Biology’s response to dieting: the impetus for weight regain

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MacLean PS, Bergouignan A, Cornier M, Jackman MR. Biology’s response to dieting: the impetus for weight regain. Am J Physiol Regul Integr Comp Physiol 301: R581–R600, 2011. First published June 15, 2011; doi:10.1152/ajpregu.00755.2010.—Dieting is the most common approach to losing weight for the majority of obese and overweight individuals. Restricting intake leads to weight loss in the short term, but, by itself, dieting has a relatively poor success rate for long-term weight reduction. Most obese people eventually regain the weight they have worked so hard to lose. Weight regain has emerged as one of the most significant obstacles for obesity therapeutics, undoubtedly perpetuating the epidemic of excess weight that now affects more than 60% of U.S. adults. In this review, we summarize the evidence of biology’s role in the problem of weight regain. Biology’s impact is first placed in context with other pressures known to affect body weight. Then, the biological adaptations to an energy-restricted, low-fat diet that are known to occur in the overweight and obese are reviewed, and an integrative picture of energy homeostasis after long-term weight reduction and during weight regain is presented. Finally, a novel model is proposed to explain the persistence of the “energy depletion” signal during the dynamic metabolic state of weight regain, when traditional adiposity signals no longer reflect stored energy in the periphery. The preponderance of evidence would suggest that the biological response to weight loss involves comprehensive, persistent, and redundant adaptations in energy homeostasis and that these adaptations underlie the high recidivism rate in obesity therapeutics. To be successful in the long term, our strategies for preventing weight regain may need to be just as comprehensive, persistent, and redundant, as the biological adaptations they are attempting to counter.

energy restriction; diet-induced obesity; obesity prone; weight loss; energy balance

IN THE UNITED STATES, OVER 60% OF ADULTS AND CLOSE TO 20% OF CHILDREN ARE OVERWEIGHT OR OBSESE (35, 174). A NUMBER OF EFFECTIVE WEIGHT LOSS STRATEGIES ARE AVAILABLE, BUT MOST ARE ONLY TRANSIENTLY EFFECTIVE OVER A PERIOD OF 3 TO 6 MO. LESS THAN 20% OF INDIVIDUALS THAT HAVE ATTEMPTED TO LOSE WEIGHT ARE ABLE TO ACHIEVE AND MAINTAIN A 10% REDUCTION OVER A YEAR (128). OVER ONE-THIRD OF LOST WEIGHT TENDS TO RETURN WITHIN THE FIRST YEAR, AND THE MAJORITY IS GAINED BACK WITHIN 3 TO 5 YEARS (3, 246). A NUMBER OF REASONS HAVE BEEN PROPOSED FOR THE HIGH INCIDENCE OF WEIGHT REGAIN (69, 246), AND SEVERAL POINT TO THE BIOLOGICAL RESPONSE TO WEIGHT LOSS.

The objective of this review is to examine the role of this biological response in the process of weight regain. Biological regulation is first discussed in relation to other nonbiological pressures that affect body weight as weight is gained, lost, and regained. The specific biological adaptations to the most common form of dieting, an energy-restricted low-fat diet, are then discussed in more detail. Previous reviews provide extensive descriptions of the normal adaptive response to energy restriction. We do not attempt to recapitulate those efforts here. Rather, the unique perspective of this review summarizes those adaptations that have been confirmed or specifically observed in the overweight or obese. Because there are unique features of the adaptive response with obesity (138, 251, 252), understanding the integrative nature of the response in the obese is pertinent to therapeutic development. Although homeostatic systems are clearly operational in both lean and obese individuals and, in both, underlie the tendency for lost weight to be regained, the central and peripheral adaptations involved in weight recovery can differ with one’s starting weight. These differences may provide insight as to what components of the homeostatic system would be most effectively targeted in those who have the most difficulty controlling their weight. To this end, we examined weight loss studies in clinically overweight and obese adults, in diet-induced, polygenic animal models of obesity, and with dietary (nonsurgical) interventions involving an energy-restricted, low-fat diet. We would assert that, in contrast to its subtle, permissive role in the development of obesity, biology has a more prominent, causal role in weight regain after energy-restricted weight loss. Countering this metabolic drive to regain lost weight may be the most significant challenge for obesity therapeutics in the coming decades.

Our Biology in the Context of Other Pressures Affecting Body Weight

Body weight is affected by biological, environmental, and behavioral pressures, all of which are inherently influenced by genetics (Fig. 1). These pressures interact with one another,
and their integrated effect establishes a “steady state” weight in adults. Humans exhibit a broad weight range, because of the variability in each of these pressures and the genetic diversity that underlies them. Changing any one of these pressures can alter the steady-state weight. To appreciate the biological influence, it is helpful to conceptualize how the homeostatic system changes with respect to these other pressures during the development of obesity, during weight loss, and during weight regain. For this purpose, we use a steady-state weight graph linked to an energy balance (Fig. 2A). The three pressures that affect body weight are positioned atop the balance, and the fulcrum of the balance represents the underlying genetic disposition. Moving the pressures to either side of the fulcrum tips the balance toward weight gain (to the left) or weight loss (to the right). The biological component (homeostatic pressures) is responsible for reestablishing a balance when the environmental or behavioral pressures change, preventing the organism from wasting away or from gaining weight indefinitely.

Over the past 50 years, our environment has become more obesogenic, favoring behavioral choices that increase the intake of energy in excess of energy requirements (99). When an individual is subjected to these pressures, stored energy accumulates, and metabolism gradually adapts to prevent perpetual weight gain (Fig. 2B). At some point, for most people, these biological adaptations reestablish a balance with the obesogenic pressures, and a new, albeit higher, steady-state weight is achieved (Fig. 2C).

In rodents, the variability in this metabolic defense against perpetual weight gain when challenged with similar obesogenic pressures (high-fat, high-carbohydrate feeding; limited physical activity) is what separates the obesity-resistant (OR) from the obesity-prone (OP) (140). Both initially experience a positive energy imbalance, but the OR sense the nutrient overload, increase fat oxidation, elevate expended energy, and reestablish energy balance (106, 107). OP rodents, on the other hand, continue to eat to excess until expenditure increases from their accumulated mass to reestablish energy balance. This polygenic predisposition for biology to respond (OR), or not respond (OP), to obesogenic pressures leads to the diet-induced obese (DIO) and the diet resistance (DR) phenotypes. The DIO/DR model is reflective of the human condition from the perspective that some people become obese and others do not, when obesogenic pressures appear to be similar. In the graphic representation, a polygenic predisposition for obesity would be akin to the fulcrum shifting right of center. If sufficiently extreme, the genetic disposition could make it practically impossible for homeostatic counter-regulatory measures to reestablish a new steady state. Weight would continue to creep up.

Fig. 1. Pressures affecting the steady-state weight. The three pressures, all influenced by the underlying genetic disposition, interact with one another, culminate in a steady state weight at which the body resides. Changing any one of these pressures can alter this steady state weight.

Fig. 2. Biology’s influence during obesity development, treatment, and relapse. Homeostatic systems adapt to prevent perpetual weight loss or gain when environmental and behavioral pressures change. The interplay of this balance between the changes in nonhomeostatic pressures and homeostatic adaptations is shown for the initial development and progression of obesity (A–C), during energy-restricted weight loss (D), during weight maintenance after weight loss (E), and during the relapse to obesity (F). Biology may play a more subtle, permissive role during the initial development of obesity, but it becomes a driving force for weight regain after weight loss.
This upward drift in weight (Fig. 2C) is observed in some DIO models. The drift occurs with some permanence in the homeostatic system, continually retuning it to target the newly achieved level of adiposity (138, 139, 148, 149). There is little evidence to suggest that circumstances would be any different for humans, when immersed in an environment with readily available foods high in fat and simple sugars and permissive to physically inactivity. Both OP-like and OR-like responses would emerge. Adding highly palatable and rewarding components to the diet recruits hedonic systems in the brain to eat even more, further challenging homeostatic systems to adapt and reestablish a steady state (136, 139). Although some weight loss can occur by returning to a lower-energy diet that is less palatable, satisfactory amounts of weight loss usually do not occur without intentionally restricting energy intake.

The most common diet is the restricted consumption of low-fat foods, which is sometimes, but not always, accompanied by regular exercise. In our graphic model, these dramatic changes in environmental and behavioral pressures initially work in concert with the biological adaptations to induce weight loss (Fig. 2D). However, the homeostatic system immediately begins to adapt to prevent the individual from wasting away. At some point, a balance is achieved at a lower, steady state weight, and the individual hits the well-known "wall" or plateau in their weight loss efforts. To lose more weight, the environmental and behavioral strategies must be stepped up a notch. To maintain the reduced weight, these weight loss strategies must be maintained indefinitely (Fig. 2E), as the homeostatic system does not appear to "reset" at this lower weight, at least in DIO rodents, even with long-term weight reduction (149). Unfortunately, most people view their weight loss program as a transient change in their lifestyle and dietary habits or have difficulty in sustaining the changes that they have made to lose the weight (52, 69). If the strategies are not maintained, the biological adaptations become a driving force for weight regain (Fig. 2F).

Two critical points emerge from this graphical description of the interplay between these pressures affecting body weight. Initially, our biology, or this homeostatic system, is actually working for us in an attempt to minimize the impact of obesogenic environmental and behavioral pressures, although with better results in OR than in OP individuals. Second, because of the upward retuning of the homeostatic system, at least for those prone to obesity, metabolic conditions after weight loss may not be the same as they were prior to gaining the weight in the first place. Instead of working in our favor to prevent weight gain, biology becomes one of the driving pressures that underlie weight regain.

Adaptations in Homeostatic Control

A complex picture of the biological system controlling body weight regulation has emerged over the last several decades. In its simplest version, it is dominated by a feedback loop between the brain and periphery. The brain receives signals from the periphery regarding energy stores (long term) and nutrient availability (short term), and on the basis of these integrated signals, adjusts energy balance to meet both the long-term storage and short-term nutrient status objectives of energy homeostasis. This feedback system adapts when energy intake is cognitively (in humans) or forcefully (in animal models) restricted, and the response, in general, promotes a positive energy imbalance, the replenishment of energy stores, and an increase in nutrient availability. Numerous components of the homeostatic system contribute to this normal physiological response. The various components are inherently linked, and the integrated adaptations work in concert. Obesity imposes additional adjustments in energy homeostasis, which make some aspects of this adaptive response distinctly different (138, 251, 252). For this reason, we limit this summary of the homeostatic adaptations to those that have been observed in the overweight or obese humans, as well as in DIO models of the human condition, in response to an energy-restricted, low-fat diet.

Adipose Signals: Low Reserves and an Empty Fuel Tank

Adiposity signals do not remain proportional to fat mass when it is changing. Two hallmarks of energy-restricted weight loss in obese and overweight individuals are a decline in fasting leptin and insulin (Table 1). Leptin and insulin have been termed "adiposity signals," because their levels generally reflect fat mass, and they convey this signal of peripheral energy storage to the brain when energy balance is maintained (16, 19). Reduced leptin levels are more intuitive, as leptin is secreted from adipose tissue. Lower insulin levels can be explained by improved insulin sensitivity (109, 124, 142, 158) and a reduced fasting and postprandial response in glucose-dependent insulinotropic polypeptide (121, 238). The low levels of leptin and insulin levels have been traditionally thought to convey a message of "depleted energy" stores to key regulatory areas in the brain (Fig. 3A). As our understanding of these hormones has increased, the role of these hormones in the homeostatic response to weight reduction has become more complex.

Recent studies have revealed that leptin, and perhaps insulin, reflects both the amount of adipose tissue and the size of the constituent adipocytes (6). Smaller adipocytes secrete less leptin and result in lower circulating levels for a given fat mass. Smaller adipocytes are also more insulin sensitive (25, 146), which presumably means they require lower circulating levels of insulin to impart the same metabolic control. Energy-restricted weight loss in the obese reduces cell size, not number (91, 148, 151, 160, 184). While total mass declines, the maximal capacity to store energy (the projected mass if all adipocytes were filled to capacity) remains the same. The decline in total fat mass and the reduced percentage of total capacity that is filled would compound the reduction in insulin and leptin. Consistent with this assertion, a number of studies have observed that leptin and insulin are reduced to a greater extent than would be expected for the amount of fat mass that is lost after weight is stabilized (110, 140, 145, 148, 196). The integrated adipose signal conveyed to the brain and peripheral tissues is, therefore, that energy reserves are low and the fuel tank is far from full (Fig. 3A).

To make the role of leptin and insulin more complex, they reflect adipose stores only when subjects are in energy balance. When an imbalance occurs, leptin and insulin reflect the metabolic state (anabolic or catabolic) of adipose tissue, as it deposits or mobilizes energy. When weight is forcefully perturbed by overfeeding, leptin and insulin are predictably elevated as weight is gained (85). However, when again allowed...
### Table 1. Effects of weight loss on adipose signals, appetite sensations, and signals of nutrient availability in obese and overweight humans

<table>
<thead>
<tr>
<th></th>
<th>PreMeal/Fasting</th>
<th>Meal/day Long/Glucose Load</th>
<th>No effect observed</th>
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<tr>
<td><strong>Adipose signals</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Insulin</td>
<td>(18, 34, 50, 51, 53, 54, 95, 97, 100, 109, 117, 133, 142, 153, 175, 196, 201, 238)</td>
<td>(42, 48, 171, 188, 193, 238)</td>
<td>(2, 94, 95)</td>
</tr>
<tr>
<td>Leptin</td>
<td>(18, 34, 50, 51, 94, 95, 97, 117, 142, 152, 153, 196, 201, 221, 228)</td>
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<tr>
<td><strong>Appetite sensations</strong></td>
<td></td>
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<tr>
<td>Hunger*</td>
<td>(4, 40, 53, 59, 61, 63, 84, 95, 238)</td>
<td>(61, 117)</td>
<td>(42, 233)</td>
</tr>
<tr>
<td>Satiety**</td>
<td>(4, 53)</td>
<td></td>
<td>(40, 42, 59, 61, 63, 84, 95, 117, 187, 233)</td>
</tr>
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<td><strong>Hunger/satiety signals</strong></td>
<td></td>
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<tr>
<td>Ghrelin</td>
<td>(18, 71, 142, 180)</td>
<td>(71, 233)</td>
<td>(18, 50, 82, 133, 142, 153)</td>
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<tr>
<td>PYY</td>
<td>(95, 121)</td>
<td>(42)</td>
<td>(143, 155, 164)</td>
</tr>
<tr>
<td>GLP-1</td>
<td>(18)</td>
<td>(1, 2)</td>
<td>(129, 175)</td>
</tr>
<tr>
<td><strong>Circulating nutrients</strong></td>
<td></td>
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<tr>
<td>Glucose</td>
<td>(1, 48, 54, 117, 133, 171, 175, 201, 219, 221, 238)</td>
<td>(1, 42, 48, 133, 153, 166, 171, 188, 219, 238)</td>
<td>(18, 53, 109, 193)</td>
</tr>
<tr>
<td>TG</td>
<td>(34, 38, 48, 53, 95, 100, 171, 181, 219, 221)</td>
<td>(48, 109, 153, 187, 213)</td>
<td>(18, 51, 142)</td>
</tr>
<tr>
<td>FFA</td>
<td>(34, 142, 221, 238)</td>
<td>(1, 42, 48, 109, 204, 238)</td>
<td>(2, 153, 166, 19)</td>
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Listed studies reflect observations in overweight and obese humans during weight maintenance after energy restricted weight loss. *Visual Analog Scale, corresponding to hunger, desire to eat, or prospective food consumption. **Visual Analog Scale, corresponding to satiety, feeling of fullness, or satisfaction with appetite.

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The two areas of the brain that are traditionally considered the homeostatic regions controlling the hypothalamic nuclei (22, 113) and the hindbrain (228). Here, we do not attempt to review in detail every region of these and other areas of the brain that are involved in weight regulation nor describe the overall picture of energy depletion. Key aspects of the overall picture of energy depletion include the expression of corticotropin-releasing hormone (137). Other projections impart modest paraventricular nucleus (PVN) reduce the expression of corticotropin-releasing hormone (137). Other projections impart modest changes, which would lead to a positive feedback on energy homeostasis, and weight gain.

The ARC projects this signal of energy depletion to other areas of the hypothalamus. In DIO models, first-order projections to the paraventricular nucleus (PVN) reduce the expression of corticotropin-releasing hormone (137). Other projections impart modest changes, which would lead to a positive feedback on energy homeostasis, and weight gain.

The arcuate nucleus (ARC) of the hypothalamus undergoes whole-cell recordings in response to an energy deficit (202), undergoing expression changes in response to an entral activity and neurotrophic signals (132, 153). Concomitant elevations in leptin in postobese rats (Fig. 4). Given that it takes several weeks of overfeeding for lost weight to return in this model, no leptin and insulin, by themselves, do not appear to sustain the signal of energy depletion as relapse progresses. Furthermore, postobese humans rarely gorge themselves continually back to obesity. Like our animal models, intermittent periods of weight stability, even though these animals experience an energy imbalance 50 to 100% higher (Fig. 4A), even though these animals experience an energy imbalance 50 to 100% higher (Fig. 4B). Later in this review, we present a novel alternative for how this energy depletion signal is conveyed during the dy-

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The drive to regain in the brain is potentiating the conveyance or reception of their energy de-

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The complete resolution of insulin and leptin in postobese rats (Fig. 4), even though these animals experience an energy imbalance 50 to 100% higher (Fig. 4A) even though these animals experience an energy imbalance 50 to 100% higher (Fig. 4B). Later in this review, we present a novel alternative for how this energy depletion signal is conveyed during the dy-

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changes in neural peptide profiles in the lateral hypothalamus (168, 252), which interfaces with the cortico-limbic system. Still other projections extend into the ventromedial hypothalamus (VMH), known for its high density of nutrient (glucose, fatty acids) sensing neurons (218). DIO rodents exhibit fewer glucose-sensing neurons in the VMH (218) and lower VMH brain-derived neurotrophic factor expression (253). Neither VMH-associated abnormality resolves after weight loss in DIO models, and their influence on weight gain may reemerge after weight loss, as other homeostatic circuits adapt to weight loss (135, 253). While the interaction between the ARC and the dorsomedial nucleus (DMN) of the hypothalamus is not clearly understood (24, 123), DMN NPY expression is higher (137) and DMN cocaine- and amphetamine-regulated transcript expression is lower (252), after weight loss from obesity. Other components of homeostatic body weight regulation in the hypothalamus may indeed be changed after energy-restricted weight loss, but they have yet to be reported in DIO models of obesity.

While confirmation of these hypothalamic adaptive responses in obese humans is difficult to come by, a plethora of indirect and genetic evidence would suggest that the hypothalamus is inherently involved in the human response to energy deficit (202). In addition, functional magnetic resonance imaging (fMRI) studies have reported altered neural activity in the hypothalamus in postobese humans, which is normalized after 3 wk of leptin replacement therapy (194). For these reasons, the hypothalamus remains a critical node for integrating and processing the homeostatic signal of peripheral energy depletion (Fig. 3A). However, we have yet to understand whether these same adaptive responses are sustained during the dynamic state of weight regain (Fig. 3B).

The hindbrain: reduced sensitivity to satiety signals. The energy depletion signal from the hypothalamus likely translates into a reduced sensitivity to satiety signals, increased meal size, and higher food intake (Fig. 3A). The nucleus of the solitary tract and area postrema are among the areas in the hindbrain that receive input via gut-derived CCK and vagal afferent signals. Monogenic obese rats that lack the leptin receptor are less responsive to CCK-induced meal size reduction, and the effects of CCK are partially restored when hypothalamic leptin receptors are generated via adenoviral gene delivery (167). Prior to the development of obesity, the hindbrain of OP rats may be less sensitive to peripheral satiety signals (39, 223). Whether this characteristic reemerges after weight loss to facilitate weight regain needs to be studied. Evidence from human fMRI studies does show weight-reduced subjects have altered neural activity in the brain stem (197), but, unlike other neural responses to weight reduction, this does not normalize with leptin therapy. Taken together, the sensitivity of the brain to gut-derived signals appears to be depressed in the obese (31), but the improved sensitivity after weight loss and during weight regain needs to be confirmed in DIO models of obesity (Fig. 3, A and B).

Integration of homeostatic and nonhomeostatic adaptations. A host of neural projections, both to and from the hypothalamus, establishes a complex network of cross talk that integrates the homeostatic system with other regions of the brain that are more traditionally considered “nonhomeostatic” (22). The effect of weight loss on these neural networks is beginning to emerge in DIO models (253). In these hedonic-cognitive areas, the reduced-obese human exhibits neural imaging responses to food-related stimuli that would favor increased motivation and drive to eat (46, 197), and many of these responses resolve with leptin therapy (197). However, it is important to recognize that communication between the hypothalamus and these nonhomeostatic areas occurs in both directions. These areas may receive peripheral signals of energy depletion or impose hedonic control to affect how homeostatic centers receive and integrate peripheral signals of energy depletion and nutrient status. Given the importance of cognitive and reward-based eating behaviors in humans (26, 47, 134), their role in the adaptive response to weight loss will continue to be studied.

Neuroendocrine signals: enhancing efficiency of fuel utilization and storage. The energy depletion signal, via the PVN in some cases, results in a number of neuroendocrine adaptations that ultimately target peripheral tissues (Fig. 3A). Energy-restricted weight loss from obesity is accompanied by a reduced sympathetic (SNS) tone (7, 110, 138, 191, 193, 221), reduced thyroid hormone levels (127, 193, 205, 228), and increased activity of the hypothalamic-pituitary-adrenal (HPA) axis (59, 157, 227, 228). In contrast to the effects on SNS, the effects on thyroid hormones and the HPA axis are observed less consistently and/or are more transiently tied to the early stages of weight loss (103, 228, 245). Collectively, the neuroendocrine changes that occur with weight loss target peripheral tissues that use and store energy, increasing efficiency to conserve energy and readying them for energy repletion (Fig. 3A). In postobese humans, leptin therapy normalizes some of these neuroendocrine responses to weight loss (191). However, more studies are needed to understand the impact of these signals on energy deposition and storage during weight regain (Fig. 3B).

The Energy Gap: Promoting a Positive Energy Imbalance

An elevated appetite. One of the primary outcomes from the neural adaptations to energy-restricted weight loss in obese individuals is an elevated appetite (Fig. 3, A and B). This is more often detected in premeal or postabsorptive appetite sensations related to hunger, desire to eat, and prospective food consumption, but it has also been observed in postprandial and day-long assessments of these measures (Table 1). Measures of hunger predict future weight regain in weight-reduced individuals (177). Surprisingly, an effect of energy-restricted weight loss on measures of satiety and satiation has rarely been observed (Table 1). This presents, to some extent, a disconnect between basic and clinical scientific communities. Studies in genetically manipulated animals have emphasized the importance of satiety and satiation in energy homeostasis, but hunger and meal initiation appear to be more important in humans and often involve nonhomeostatic cues or motivations. Some of this discrepancy may be due to the difficulty in making a clear distinction between hunger and satiety in laboratory animals. In contrast to the food questionnaires used to gauge hunger in humans prior to a meal, animal studies often simply measure how much food is eaten when food is made available. The overeating that occurs may result from increased hunger and/or a delay of (or a modification of) satiation. However, the more substantial difference between human and animal studies are the nonbiological pressures affecting body weight (Fig. 1),
which can work with or against the biologically driven appetite (Fig. 2).

Humans are motivated by psychosocial pressures, with varying degrees of success, to keep weight off. The characteristics of cognitive restraint, disinhibition, and susceptibility to hunger, can affect energy intake (186) and measures of hunger and satiety (89). Those who actively seek out weight loss, and thus more likely to enter a weight loss study, exhibit more restrained eating behavior (27). Moreover, individuals who do lose weight exhibit increased cognitive restraint, lower disinhibition, and lower susceptibility to hunger (2, 40, 42, 76, 114, 179, 247). These cognition-driven eating behaviors undoubt-
edly lead to variability in the assessment of biology’s overall impact and may explain why humans often exhibit different patterns of hyperphagia during postobese weight regain (240). It would be a mistake, however, to discount biology’s influence because the presence of these psychosocial pressures makes it difficult to measure.

The picture of biology is much clearer in postobese DIO rodents, which are not subject to the same complex psychosocial influences and environmental variability. Driven mostly by their biological urges, these models consistently show that appetite increases such that they want to eat well in excess of what they were eating before they lost weight (17, 65, 104, 137–139, 148, 151), an effect on appetite that persists until the lost weight is regained. An increase in meal size, rather than number, is involved in the development of the DIO phenotype (73) and in the hyperphagia following energy restriction in normal weight animals (55). We suspect the same will be reported in the DIO during weight regain.

**Suppressed energy expenditure.** The significance of the adaptive response in energy expenditure has been less appreciated and somewhat confounded by the lack of consensus on how to normalize and interpret data. The confounding issues include: 1) the methods used to adjust for the loss of tissue that contributes to basal energy requirements; and 2) what body compartments (fat mass, lean mass, both) should be used as the estimated amount of tissue that contributes to basal energy requirements. The recent emergence in preclinical research communities of regression analysis for normalization (5, 33, 112, 149) may help to resolve the first issue. Although this approach has been the general standard in clinical research for some time, its application in animal research has been relatively rare. On the other hand, clinical researchers continue to include fat mass in their regression models to correct for the decline in basal tissue energy requirements when studying metabolic efficiency. The recent work of Kaiyala et al. (112) provides strong evidence that the primary impact of fat mass on energy expenditure is not in its contribution to the basal energy requirements for tissue maintenance, but instead regulatory in nature, as a node in the homeostatic feedback loop controlling body weight. These recent developments should bring both research communities together and move this field toward a unified gold standard for the presentation and interpretation of metabolic data (147).

What is often overlooked because of the aforementioned confusion is the most fundamental adaptation and its implications: total energy expenditure declines (Fig. 3, A and B). This adaptation to weight loss has been shown in numerous studies of overweight and obese humans (8, 60, 62, 131, 132, 159, 189, 192, 196, 242–244) and in polygenic models of obesity (45, 65–67, 148–151, 199), and every component of energy expenditure is affected to some extent (Fig. 5). The mechanisms are linked to both the loss of body mass and enhanced metabolic efficiency.

The lower body mass contributes to the decline in expended energy in three ways. First, there is often less lean mass contributing to the basal tissue maintenance costs of the organism. This manifests in a reduced basal metabolic rate (resting energy expenditure, REE), reported for both obese humans (8, 60, 70, 77, 78, 80, 102, 132, 159, 189, 192, 234, 245) and obese animals (45, 66, 149–151) after energy-restricted weight loss. Second, less total mass must be moved during physical activity, so the same activity will be less energetically expensive. If activity levels are the same, this is observed as a decline in the nonresting component of energy expenditure (NREE), which has also been consistently reported after weight loss (66, 132, 191, 192, 196, 242–244). Finally, the loss in fat mass reduces energy expenditure, primarily by altering metabolic efficiency via its role in homeostatic regulation (i.e., reduced leptin, insulin) (112).

This regulatory effect on efficiency affects both basal metabolism and the energy expended during physical activity. The majority of studies show that a portion of the decline in REE remains significant after adjusting for the loss in lean mass (8, 45, 60, 65, 66, 70, 102, 132, 149, 150, 234). The enhanced work efficiency during physical activity impacts both nonexercise and exercise activity thermogenesis (66, 198), at least with activity at lower levels of intensity. These effects ultimately reduce NREE, when activity levels are the same. Leptin therapy reverses these adaptive responses in postobese humans (191, 195).

A more fundamental biological adaptation may occur to reduce NREE by simply reducing the amount of activity. In stark contrast to most rodents (202), DIO rats that have lost weight lower their volitional wheel running (137) and exhibit reduced compliance to daily treadmill exercise during weight regain (151). These observations suggest a reduced biological
drive to be physically active, which may be rooted in homeostatic neural pathways that involve the orexin system (126). These neuronal pathways are altered in OP rats, and the lower intrinsic activity levels are thought to contribute to their DIO phenotype when fed a high-fat diet. It is unclear how the orexin neurons and their targets are altered in DIO models after weight loss, but we suspect that at least the preexisting defects are likely to reemerge. Some clinical studies have shown a decline in activity during weight loss (241, 242). However, physical activity and the desire to be physically active, like appetite sensations, are difficult to directly measure in humans. Similar to nonhomeostatic influences of food intake, humans are motivated to increase physical activity in their cognitive pursuit of a lower weight and better health. Success is variable, however, as compliance to exercise prescriptions in combination with dieting is notoriously poor (36). Additional studies are needed to clarify whether reduced activity, or reduced motivation to be physically active, in postobese individuals is indeed part of the biological response to weight loss.

Finally, NREE also declines because less food is consumed. Less food requires less energy for ingestion, absorption, metabolism, and storage, and the consequence is a lower thermic effect of food after energy-restricted weight loss (159, 243). Beyond this predictable change related to the amount of food, however, ingested food can also induce thermogenesis by increasing sympathetic tone (224). Some studies have reported that this facultative thermogenesis, particularly with respect to glucose-induced thermogenesis, declines after energy-restricted weight loss (86, 235), but other studies show the effect is not sustained with long-term weight reduction (132, 235). Regardless, the adaptations, if any, that do persist may be inherently linked to the same mechanisms that underlie enhanced metabolic efficiency at rest and during exercise.

In summary, the reduction in mass and ingested energy, the enhanced metabolic efficiency, and any decline in activity levels, all contribute to lower expended energy (Fig. 3A). Studies in rodents have shown that this hypometabolic state persists during weight regain (Fig. 3B), normalizing only after the lost weight returns or, in some cases, the original weight is surpassed (67, 137, 148). Because much of this effect can be explained by reduced mass, the relevance of this biological response in energy expenditure is often discounted. However, the brain does not reset the appetite to match the lower-energy requirements of the remaining tissue. The lower-energy requirements, whether from the loss of lean tissue or from increased efficiency, become a quantifiable burden that must be overcome in the pursuit to maintain the reduced weight. This may be why the decline in energy expenditure, similar to the elevated hunger, is predictive of weight regain (156).

The energy gap: biology’s drive to go off a diet. Because both sides of the energy balance equation are affected after weight loss, the biological pressure to gain weight is a consequence of both increased appetite and suppressed energy expenditure. We have termed this difference between appetite and expenditure requirements the “energy gap” (108, 148, 231).

![Fig. 4. Effect of dietary fat on the resolution of insulin and leptin and the energy gap at the maintenance-relapse transition. A: insulin and leptin, expressed as a percentage of obese controls, are shown for energy-restricted, weight-maintained rats before (weight reduced and in energy balance) and after the first day of relapse. Data were drawn from three similar DIO rat weight loss studies of relapse on diets containing 12%, 25%, and 40% kcal fat. B: energy gap at this transition from weight maintenance to relapse is estimated from the positive energy balance on the first day of relapse. (Data were adapted from Am J Physiol Regul Integr Comp Physiol 294: R1117–R1129, 2008 and two similar ongoing studies with higher levels of dietary fat (n = 6–10/group)). *Significantly different from 12% kcal fat diet, P < 0.001.]

![Fig. 5. Impact of weight loss on the components of total energy expenditure (TEE). Energy-restricted weight loss impacts every component of energy expenditure. The absolute levels of resting energy expenditure (REE) decline from a loss of metabolic mass and enhanced metabolic efficiency. Nonresting energy expenditure (NREE) declines, unless the level of physical activity and its associated exercise activity thermogenesis (EAT) are substantially increased. This increase must overcome the decline in the TEF that results from lower energy consumption and a decline in nonexercise activity thermogenesis (NEAT) related to loss in overall mass. Increased energetic efficiency of EAT, NEAT, and potentially TEF contribute to the overall decline in NREE.]

AJP-Regul Integr Comp Physiol • VOL 301 • SEPTEMBER 2011 • www.ajpregu.org
In humans, it is difficult to quantitatively measure appetite in terms of energy equivalents, so accurately estimating the energy gap becomes challenging. In lieu of this difficulty, the energy gap has also been discussed as the difference between pre-weight loss energy requirements and post-weight loss energy requirements (101). We would suggest this is a conservative estimate of biology’s impact, as animal studies clearly show that the energetic equivalent of “appetite” more than surpasses the energy requirements of the obese state. In animal models, both components of this energy gap can be directly measured by assessing energy balance in the weight-reduced state and during a subsequent day of ad libitum feeding (108, 151).

During weight maintenance after weight loss, this energy gap reflects the magnitude of the daily burden that thwarts cognitive efforts to maintain the reduced weight. Our studies indicate that this energy gap at the maintenance-relapse transition is influenced by diet composition (Fig. 4B), by the length of time in weight maintenance after weight loss (149), and by physical activity levels (151). The relative contribution of the adaptations in appetite and expenditure can vary between and even within animal models (92, 93). Regardless of which side of the energy balance equation is most affected, the energy gap imparts a substantial pressure to eat in excess of the energy requirements. Obese humans may exhibit this same variability (240), which could explain the common observation of “responders” and “nonresponders” in clinical studies focused only on one side of the energy balance equation.

Finally, studies in obese humans and rodents suggest that weight regain reflects a first-order growth curve (3, 148, 151). The rate of gain, and, therefore, the energy gap and the energy imbalance it promotes, diminishes during the relapse to obesity as a function of this first-order relationship. In addition to diet and physical activity, both the amount of weight lost and the time in weight maintenance may influence this relationship. The magnitude of the energy gap is greatest at the nadir weight after weight loss (108, 148, 151). Likewise, this energy gap does not dissipate with time in weight maintenance. Rather, studies in DIO models indicate that the magnitude of the energy gap gradually increases the longer they maintain their reduced weight with an energy-restricted diet (149). The implications from these observations are that the biological pressures may strengthen with time and the amount of lost weight, gradually increasing their perceived influence.

The Gut: Sensing the Prandial State

The gut plays a critical role in the homeostatic body weight regulation, as it is the origin of a number of neural, nutrient, and hormonal responses to ingested energy. These gut-derived signals of the nutrient status are reviewed in more detail elsewhere (74, 115, 249). In general, if these signals change in the obese humans in response to energy-restricted weight loss, a collective signal favoring hunger over satiety/satiation is observed (Table 1). However, detection of this adaptive response is much less consistent than that of circulating adipose signals and nutrients, as they may be dependent on the presence of a negative energy balance (2, 30, 42, 71, 133), the amount of weight loss (71), the amount of physical activity (121), the specific derivative of the hormone measured [peptide YY(PYY) vs. PYY3−36; total vs. acetylated ghrelin] (18) or the type of macronutrient restricted in the diet (71, 95). Even under the same conditions of weight loss and maintenance, there is a wide variability in individual responses with respect to these adaptations in hunger and satiety signals (18). As such, these adaptations may be more or less influential, depending upon the genetic disposition and diet composition.

When they do persist into weight maintenance, these altered signals could potentiate the effects of a brain that may already be more sensitive to hunger signals and less sensitive to satiety signals (Fig. 3A). They may also act in the periphery to indirectly alter food intake, insulin secretion, gastric emptying, fuel utilization, and energy expenditure (14, 203, 249, 255). Less is known about vagal afferent signals and a large number of other humoral factors known to regulate appetite and energy balance (88, 178), as they have yet to be studied in the obese after weight loss or during weight regain (Fig. 3, A and B).

Changing gut microbiota-emerging implications for nutrient absorption. The effect of obesity on gastric emptying is unequivocal (98), but some studies show that emptying of solids may be slowed after weight loss (155, 229, 237). Other studies show little effect of weight loss (105). Regardless, the effect in humans appears to be transient, such that it does not persist with long-term weight reduction.

More attention in recent years has been directed to gut microbiota (231). Energy-restricted weight loss results in an increase in the proportion of Bacteroidetes/Firmicutes bacteria in some studies (141, 170) and a diet-dependent reduction of butyrate, producing Firmicutes bacteria in others (68). The implications and relevance of these adaptive responses in gut microbiota are as yet unclear, but there is evidence that microbiome alterations like these can affect energy extraction, metabolism, and adiposity (10, 11, 169). It remains to be seen whether the altered gut microbiota after energy-restricted weight loss contributes weight regain in obese humans, or is simply coincidental to changes in diet.

Enhanced Metabolic Flexibility: Improved Nutrient Clearance

Improved metabolic regulation. Metabolic inflexibility refers to an organismal impairment in regulation, which manifests as the inability to appropriately shift fuel preference in the face of metabolic challenges, like fasting, exercise, a meal, or overfeeding (119, 120, 220). The inflexible state of metabolism results from a discordant attempt of numerous peripheral tissues to respond to changing fuel needs and nutrient availability, yielding little or no discernable response. Metabolic inflexibility is a common characteristic of obesity (119, 220), and energy-restricted weight loss reverses many of its associated impairments in metabolic regulation (48, 81, 158, 188, 219). Because enhanced metabolic flexibility improves the metabolic response to ingested energy, it alters the peripheral signals of nutrient status that are sent to the brain during weight maintenance and during weight regain (Fig. 3, A and B). Because lean subjects do not generally exhibit this global impairment in metabolic regulation, the extent to which an improvement in whole body responses to metabolic challenges, like overfeeding, contributes to the general response to calorie restriction is unclear. For the obese, enhanced metabolic flexibility, like other nodes in homeostatic regulation, may sustain the energy
The normal response to a meal or overfeeding, which includes suppressing fat oxidation and increasing carbohydrate oxidation when carbohydrates are sufficiently high in the diet, reemerges after weight loss (12, 23, 108, 149, 150, 187, 211). Dietary fat is preferentially trafficked to adipose and hepatic triglyceride stores rather than being used for energy needs. This enhanced metabolic response to ingested nutrients occurs, in part, from an increase in whole body insulin sensitivity (109, 124, 142, 148, 158). While beneficial for metabolic health, the enhanced insulin sensitivity primes the body for rapid, energetically efficient weight gain during chronic overfeeding (148, 230). As long as the weight-reduced subject restricts intake and stays in energy balance, there is little impact of enhanced metabolic flexibility on 24-h substrate oxidation (32, 150, 151). However, the rapidity and efficiency of nutrient clearance could reasonably hasten the transition to a postabsorptive state, the reemergence of hunger pains, and the persistence of the energy gap.

When overfeeding occurs, the improved response to ingested energy transitions into a sustained suppression of fat oxidation and the trafficking of dietary fat to adipose tissue (108), ensuring the most efficient repletion of adipose stores (75, 210). The energetic cost of depositing excess dietary fat into triglyceride depots is much less than an equivalent carbohydrate or protein (~<2% vs. ~25% of the energy excess) (209). For protein and carbohydrate, additional energy is required to pay for converting these nutrients into fat via de novo lipogenesis. In DIO models, the preferential deposition of dietary fat is observed even in minor bouts of overfeeding, ensuring weight gain occurs at the highest rate and with the greatest energetic efficiency (108). This increased rate and efficiency of weight gain may explain, in part, why weight regain is predicted by improved insulin sensitivity (250), an enhanced response to a glucose load (28), and the preferential use of carbohydrate for energy production (80).

Nutrient availability declines. Improved insulin sensitivity is often accompanied by lower fasting levels of glucose, free fatty acids (FFAs), and triglycerides (TGs) in circulation (Table 1), but more consistently yields reduced postprandial excursions of glucose and TGs with potentiated postprandial reductions in FFAs (Table 1). These effects are often reflected in lower fasting levels of these nutrients as well (Table 1). This whole-sale, consistent change in circulating nutrients undoubtedly imparts some homeostatic influence on the signals of nutrient status (Fig. 3A). Levels of glucose are detected by nutrient-sensing systems in both the periphery (15, 41, 56, 130, 212) and brain (111, 130), with consequences to energy balance and fuel utilization in the periphery. TGs may even be sensed via sensing systems in both the periphery (15, 41, 56, 130, 212) and during weight regain (108). With every meal, every bout of overfeeding, and sustained periods of a positive energy balance, the suppressive effects of FFAs on the energy gap would be minimized. As such, FFAs represent one signal of nutrient status after energy-restricted weight loss that could sustain a message of nutrient deprivation during the dynamic metabolic state of weight regain (Fig. 3B). Later in this review, we connect this aspect of FFA metabolism to peripheral energy repletion and the energy gap.

Liver: Restored Function of a Transient Energy Depot

The nutrients and hormones discussed earlier in this review are known to act directly on the liver (43), and their changes after weight loss have dramatic effects on hepatic metabolism. Relief from the persistent nutrient overload that accompanies the development and progression of obesity could alone improve metabolic regulation in the liver. However, the decline in leptin and insulin is also likely involved, as they support the expression of catabolic and anabolic genes, respectively, in this tissue (29). In addition, an emerging body of evidence suggests that hepatic metabolism is also subject to hypothalamic regulation (20, 83, 165, 182, 183), which needs to be studied in obesity models after energy-restricted weight loss. While our focus is on the overweight and obese, the majority of the adaptations in the liver can be extended to energy restriction in general. As obese individuals are less glucose tolerant with a higher incidence of steatosis than the lean, these adaptive responses may appear to be more dramatic in the overweight and obese.

The nutrient, hormonal, and potentially neural changes that occur with weight loss from an obese state result in a global reduction in hepatic gene expression (100), and this is accompanied by reduced markers of protein synthesis (214). These adaptations are indicative of a gross reduction of this tissue’s energy requirements, undoubtedly contributing to the reduced basal energy requirements measured over the whole body (Fig. 3A). The liver’s regulation of both carbohydrate and lipid metabolism improves within as little as 48 h of an energy deficit (124), and this improvement persists into weight maintenance (109, 124). Hepatic lipid declines (38, 124, 219), splanchnic glucose uptake increases (206), and glucose production is reduced (124). Secretion of very low density lipoproteins, ApoB-100 particles in circulation, and hepatic-triglyceride lipase, declines (38, 116). In postobese rodents, the suppression of dietary fat oxidation during the dark cycle (when they feed) is reversed later in the light cycle when their energy balance provision of food is gone (108). The return of this diurnal cycle of anabolic and catabolic states reflects the restored function of a transient depot for ingested energy, which can facilitate the rapid clearance of nutrients during bouts of overfeeding (Fig. 3B).

Sustained periods of overfeeding lead to the induction of genes associated with de novo lipogenesis, similar to what is observed in the “catch-up” fat phenomenon in younger animals (49). In our postobese rats, de novo lipogenesis is readily apparent within 12 h of overfeeding, and a substantial retention of this newly formed fat is observed in the liver after 24 h (108). Studies in humans suggest that when hepatic regulation is intact, as it is after weight loss, chronic overfeeding of a low-fat, high-carbohydrate diet leads to the trafficking of
glucose to fat depots rather than glycogen pools (161, 162). This is consistent with what is observed in postobese rats during the early stages of weight regain (108). Once converted to fat, this energy cannot be remobilized to support glucose homeostatic objectives. The implications are that the transition to the postabsorptive state would be hastened and the peripheral signal of low nutrient availability promoting further overfeeding would be sent sooner.

**Skeletal Muscle: Reduced Energy Requirements and A Preference for Carbohydrate**

The same neural, endocrine, and nutrient signals affecting the liver also reduce the energy requirements of skeletal muscle, which has a more substantial impact on daily expended energy because of its overall mass. This increased metabolic efficiency is a general characteristic of the adaptive response to energy restriction and occurs to some extent in all animals, regardless of their adiposity level. What may be different for the obese is the impact on fuel utilization. Like hepatic de novo lipogenesis, adaptations in skeletal muscle facilitate the clearance and dissipation of excess carbohydrate, as glucose becomes the preferred fuel under postprandial conditions (Fig. 3A). Metabolic regulation improves in skeletal muscle, as insulin’s stimulation of glucose uptake and its suppression of fat oxidation are enhanced (48, 118, 207, 226). As lean subjects generally have muscles that are more insulin sensitive and already exhibit this preferential use of fuels in response to overfeeding, the shift in fuel utilization and its impact on nutrient clearance may be less apparent. For the obese, the improvement in metabolic regulation could have consequences during maintenance and regain. When energy balance is maintained by cognitive (humans) or forced (animals) restriction, enhanced insulin sensitivity has little effect on 24-h substrate balance or weight gain (32), but the increased clearance rate of circulating nutrients and lower nutrient availability could help create the large energy gap between appetite and expenditure requirements during weight maintenance (Fig. 3A). When overfeeding occurs, more discernible effects on energy balance have been observed (108, 151), as the fuel preference of this tissue ensures that carbohydrate loads are rapidly dissipated through oxidation, and excess nutrients are stored in an energetically efficient manner (Fig. 3B).

While the improvement in insulin sensitivity in muscle is responsible for this postprandial fuel preference, the critical energy sensor in muscle, AMPK (200), also becomes more responsive. Its regulation by leptin, insulin, and sympathetic neural efferents is impaired in DIO models of obesity (154), and some aspects of AMPK regulation appear to resolve after energy-restricted weight loss (81, 108). This fuel preference may be exacerbated by an inherent impairment in the capacity to oxidize fat, which underlies the genetic predisposition for obesity (106, 107). Unlike lean subjects, energy-restricted weight loss in obese subjects fails to increase skeletal muscle oxidative capacity (215, 225, 226) unless the energy-restricted diet is accompanied by regular exercise (96, 207, 208). Mitochondrial respiratory capacity declines (188), glycolytic capacity declines (87, 215), and the expression of enzymes associated with β-oxidation and mitochondrial enzyme activities remain low and, if anything, decline (62, 188, 215, 225). Collectively, these adaptations in muscle underlie the reduced energy requirements, the increased metabolic efficiency, and the enhanced muscle work efficiency observed with energy-restricted weight loss in postobese subjects (192, 198) (Fig. 3A). These adaptations also limit the body’s capacity to dissipate excess fat when overfeeding occurs (Fig. 3B).

**Adipose Tissue: an Expanding, Empty Fuel Tank, Primed for Filling**

Like the liver, adipose tissue experiences a global down-regulation of metabolic gene expression in response to energy-restricted weight loss (34). Unlike the liver, much of this adaptation is reversed at the transition to weight maintenance, favoring a gene expression profile that would enhance energy conservation during weight maintenance and the repletion of energy stores during meals or periods of chronic overfeeding (21, 34, 90, 122, 125, 222, 239). Markers of oxidative stress and inflammatory cytokines, which are also known to suppress appetite and increase expenditure, decline (104, 122, 176). The impaired induction of lipogenesis by insulin, glucose, and feeding associated with obesity (57, 58, 64, 162) resolves after energy-restricted weight loss (72, 108, 122, 172, 204). The enhanced metabolic response to ingested energy enhances nutrient clearance during weight maintenance (Fig. 3A) and during sustained periods of overfeeding (Fig. 3B).

The reduction in average adipocyte size rather than a decline in cell number (91, 148, 151, 160, 184) likely contributes to the improved metabolic regulation in this tissue. Total capacity of the tissue to store fat remains the same, but stored energy falls well below capacity (Fig. 6A). Regardless of overall adiposity, smaller adipocytes, compared with larger adipocytes, are more sensitive to the antilipolytic effects of insulin, exhibit a lower basal and catecholamine-induced lipolysis, have a lower rate of turnover of the stored lipid, and express genes favoring energy storage (25, 146, 222). Reducing the size of adipocytes with energy-restricted weight loss primes them to take up and store excess energy when overfeeding occurs. This would presumably contribute to the metabolic drive to regain weight for both lean and obese subjects.

The impact on nutrient clearance may be further exacerbated by the formation of new adipocytes (Fig. 6B). Our studies of weight regain in DIO rats that are prone to obesity revealed the emergence of a population of very small (<20 μm) adipocytes during the early stages of weight regain. Their appearance was accompanied by an increase in total number of adipocytes in the depot (108). As weight gain proceeded, preferential hypertrophy of these small cells was observed, while the higher cell number persisted (Fig. 6C). By 10–14 days of relapse, the small cells become indistinguishable from the preexisting adipocytes in the fat pad. As the relapse to obesity continues, hypertrophy occurs more broadly across the entire depot (Fig. 6D), and the increase in cell number continues to persist. Most animals in this DIO model gain more weight than they originally lose before the rate of gain normalizes (148, 151). Yet, after surpassing their previous weight, these relapsed animals still have smaller adipocytes on average and more adipocytes per fat pad than an obese rat that had never lost or regained the weight (Fig. 6E). While substantiating the temporal changes in cell size frequency distribution and total cell number in humans presents a substantial challenge, a hypercellularity phenomenon with similar characteristics has been reported in postobese humans (145). Even so, this relapse-induced hyper-
plasia of adipose tissue, if it does occur, is likely limited to individuals who have a genetic predisposition for obesity. We have yet to observe an increase in cell number in DR rats or in DIO mice, which tend to relapse to their previous weight. If this does occur in some humans, particularly those who are obese or are prone to obesity, the consequences lie not only in facilitating rapid, energetically efficient regain early in relapse (Fig. 3B), but also in permanently expanding the total storage capacity of the depot.

An Integrated Picture of the Biological Drive to Regain Weight

No single adaptation that we have discussed provides a stand-alone explanation for biological drive to regain weight after weight loss. These adaptations are interdependent and integrated, establishing a system filled with redundancy. Comparing Fig. 3, A and B, it is clear that we have a better understanding of the homeostatic adaptations that are observ-
able during weight maintenance after weight loss. Considerably less is known about the signals that sustain the energy gap during dynamic metabolic states when the well-known adipose signals, leptin and insulin, do not reflect levels of stored energy in the periphery. From the information presented in this review, we have developed one model of how this message is sustained during the relapse process.

The nutrient clearance model for the dynamic metabolic state of weight regain. The model we propose suggests that the energy-depletion signal from adipose tissue is inherently linked to the cellularity characteristics of adipocytes in the body and is conveyed to the brain by the levels of circulating nutrients (or their neuroendocrine surrogate signals) during postprandial, anabolic conditions (Fig. 7). Energy-depleted adipose tissues have smaller adipocytes with an exceptionally high capacity to clear ingested energy from circulation (Fig. 7, A and B). This capacity would be further enhanced if very small, new fat cells appear at the maintenance/relapse transition (Fig. 7C). The enhanced clearance rate of adipose tissues would attenuate postprandial glucose excursions and potentiate the postprandial suppression of circulating FFAs. During sustained periods of overfeeding, the link between adipocyte-specific nutrient clearance and circulating levels would become stronger, as storage depots in other tissues (liver, muscle, etc.) fill to capacity. The blunted glucose excursions and suppressed FFAs levels during this sustained, anabolic state may then be sensed by the brain directly, via hypothalamic nutrient sensing neurons, or indirectly, via neuroendocrine signals reflecting nutrient status.

With this model, the adipose tissue’s capacity to clear excess energy is pitted against the rate at which nutrients are ingested and absorbed. Excessively large bouts of overfeeding may temporarily overwhelm the clearance rate, elevating glucose to the extent it negatively affects appetite despite FFAs levels remaining suppressed. When adipose tissues eventually catch up, circulating glucose and its associated neuroendocrine markers would decline, appetite would increase, and additional bouts of overfeeding would ensue. At some point, a regular, sustained supply of energy would be achieved to match the high clearance rate of adipose tissues. As the adipocytes expand, their capacity to clear excess energy diminishes and the suppressive effects on circulating nutrients under dynamic (postprandial) states of metabolism would decline. If adipocyte hyperplasia occurs early in relapse, as it does in our DIO rats, relapsing to the previous weight would return the animal to the same fat mass, but the adipocytes on average would be smaller (Fig. 7D). Rates of nutrient clearance would remain somewhat elevated and the impact on postprandial nutrients would persist, gradually declining as the adipocytes become larger, more

![Fig. 7. Model linking adipocyte cellularity and peripheral nutrient clearance to the energy gap during dynamic weight regain.](Image)

For reference, weight and cellularity characteristics from the studies presented in Fig. 6 are shown for each stage of weight loss and regain (A–C, E). This model suggests that the energy-depletion signal from adipose tissue is inherently linked to the cellularity characteristics of adipocytes in the body and is conveyed to the brain by the levels of circulating nutrients (or their neuroendocrine surrogate signals) during postprandial, anabolic conditions (Fig. 7). Energy-depleted adipose tissues have smaller adipocytes with an exceptionally high capacity to clear ingested energy from circulation (Fig. 7, A and B). This capacity would be further enhanced if very small, new fat cells appear at the maintenance/relapse transition (Fig. 7C). The enhanced clearance rate of adipose tissues would attenuate postprandial glucose excursions and potentiate the postprandial suppression of circulating FFAs. During sustained periods of overfeeding, the link between adipocyte-specific nutrient clearance and circulating levels would become stronger, as storage depots in other tissues (liver, muscle, etc.) fill to capacity. The blunted glucose excursions and suppressed FFAs levels during this sustained, anabolic state may then be sensed by the brain directly, via hypothalamic nutrient sensing neurons, or indirectly, via neuroendocrine signals reflecting nutrient status.
insulin resistant, and less capable of clearing excess energy. As adipocytes become filled to capacity, postprandial glucose excursions would reflect those prior to weight loss and postprandial suppression of FFAs would be abolished. The high levels of these nutrients, or their neuroendocrine mediators, would feed back to the brain, minimize the energy gap, and normalize the rate of weight gain (Fig. 7E).

This “nutrient clearance” model is generally consistent with preclinical and clinical observations of energy-restricted weight loss from the obese state, providing a reasonable picture of how the energy gap is sustained as weight regain occurs. However, we acknowledge that it is not substantiated, nor is it likely to be substantiated, at every step with definitive proof. As highly integrated as body weight regulation is, biology’s drive to regain lost weight will certainly not be this simple and straightforward. Even so, the model serves the purpose of placing the focus on the dynamic metabolic state associated with the sustained positive energy imbalance. We have presented circulating nutrients as the conveyor of this message, but changes in proinflammatory cytokine secretion from adipose tissue provide an equally plausible mediator coincident to cellularity and postprandial nutrient levels in the blood. Alternatively, neural afferents projecting into critical energy balance neural networks in the brain (15, 217) may sense and convey the signal of energy depletion in a more direct manner. While these and a number of other possibilities should be considered, maintaining the focus on the dynamic metabolic state during the process of weight regain will be important to advance our understanding of the process of weight regain.

Perspectives and Significance: Countering the Biological Drive to Regain Weight

While the homeostatic influence on body weight plays a more subtle, permissive role in the development of obesity, biological, permissive emerge after weight loss to impart a more prominent influence on the process of weight regain (Fig. 2). It is the dieting and the deviation from the “steady-state” weight that awakens the body’s defense system. The biological response is persistent, saturated with redundancies, and well focused on the objective of restoring the body’s depleted energy reserves. Any weight loss strategy that fails to acknowledge and plan for this emerging metabolic influence is likely to have little success in facilitating long-term weight reduction.

Even so, the overarching message about our biology’s response to weight loss should not be misconstrued into a conciliatory surrender to the inevitability of weight regain. The biological drive to regain lost weight can be countered with environmental, behavioral, and pharmaceutical interventions (Fig. 2E). Composition of the weight maintenance diet (high protein, low carbohydrate; type of dietary fat) has a significant impact on several aspects of this homeostatic response (9, 37, 216), as does the amount of physical activity and regular programmed exercise (137, 151). Promising combination pharmacotherapy, targeting more than one component of the homeostatic system is also on the horizon (190). By acknowledging that these homeostatic pressures emerge, we can proactively develop and implement regain prevention strategies to counter their influence. To ensure success, the regain prevention strategies will likely need to be as comprehensive, persistent, and redundant, as the biological adaptations they are attempting to counter.

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