Increasing Adiposity
Consequence or Cause of Overeating?

Ninety years ago, an editorial in *JAMA* questioned the prevailing approach to obesity treatment: “When we read that ‘the fat woman has the remedy in her own hands—or rather between her own teeth’...there is an implication that obesity is usually merely the result of unsatisfactory dietary bookkeeping...[Although logic suggests that body fat] may be decreased by altering the balance sheet through diminished intake, or increased output, or both...[t]he problem is not really so simple and uncomplicated as it is pictured.” Since then, billions of dollars have been spent on research into the biological factors affecting body weight, but the near-universal remedy remains virtually the same, to eat less and move more. According to an alternative view, chronic overeating represents a manifestation rather than the primary cause of increasing adiposity. Attempts to lower body weight without addressing the biological drivers of weight gain, including the quality of the diet, will inevitably fail for most individuals. This Viewpoint summarizes the evidence for this seemingly counterintuitive hypothesis, versions of which have been debated for more than a century.

**Physiological Mechanisms**

Voluntary changes in calorie intake predictably produce short-term weight change, suggesting the possibility of conscious control of body weight over the long term. However, feeding studies demonstrate that changes in energy balance produce biological adaptations that antagonize ongoing weight loss or gain. For instance, in a study in which 41 lean or obese research participants were underfed or overfed to achieve 10% to 20% weight change, energy expenditure decreased or increased, respectively. These metabolic responses and reciprocal changes in hunger serve to defend baseline body weight. Indeed, only a small proportion of overweight and obese people in the United States report ever having maintained weight loss of at least 10% for 1 year.

**Metabolic Fuel Concentration, Hunger, Body Weight**

The body has a continuous energy requirement, and for this reason, the concentration of major metabolic fuels—glucose, nonesterified fatty acids, and ketones—is tightly controlled, with their combined total ranging in the plasma between 4 and 6 kcal/L, according to one study of 8 obese young adults. An acute decrease in the circulating concentration or oxidation of these fuels provokes intense hunger and food intake. Conversely, pharmacological manipulations that increase metabolic fuel availability, such as fatty acid synthase inhibition or β3 agonist administration, lower food intake. Disorders involving the anabolic hormone insulin highlight the potential influence of metabolic fuel concentration on body weight regulation. Insulin drives glucose and nonesterified fatty acids into storage forms through coordinated effects on carbohydrate and fat metabolism. States of increased insulin action, such as excessive insulin treatment in diabetes and insulinoma, predictably cause weight gain, whereas decreased insulin action (eg, insulin omission in type 1 diabetes) results in weight loss.

**Metabolic Defects May Precede Overeating in Obesity**

In experimental models, obesity may arise from genetic manipulation of energy homeostasis pathways throughout the body that do not affect food intake, including muscle-specific insulin receptor ablation, adipose-specific overexpression of 11β-hydroxysteroid dehydrogenase type 1 (an enzyme involved in glucocorticoid metabolism), and liver-specific overexpression of sterol regulatory element-binding protein-1c (a transcription factor regulating de novo lipogenesis). Of particular relevance, changes in dietary composition can produce obesity in genetically normal animals, independent of an increase in calorie intake. Rats fed high vs low glycemic index diets developed hyperinsulinemia, increased expression of fatty acid synthase in fat tissue, and greater incorporation of glucose into lipids—metabolic abnormalities that predispose to excessive fat deposition. When the high glycemic index animals were food-restricted to prevent excessive weight gain, they still gained substantially more fat (70%) than the low glycemic index animals and also exhibited adverse changes in cardiovascular disease risk factors.

This combination of increased adiposity despite reduced energy intake cannot be explained by the calorie-centric view of obesity but may be understood by the alternative model. Various genetic or environmental factors, including the quality of the diet (Figure), induce an excessively anabolic state that favors storage rather than oxidation of ingested calories (ie, increased lipogenesis, avid uptake of glucose and lipid into fat cells, and lower fasting lipolysis and insulin resistance in muscle). Subsequently, hunger increases and energy expenditure decreases, reflecting the body’s attempt to compensate for the loss of circulating metabolic fuels sequestered into adipose tissue and therefore unavailable for other metabolic requirements.

**A Focus on Diet Composition, Not Total Calories, May Best Facilitate Weight Loss**

If anabolic metabolic defects precede and promote overeating, then conventional calorie-restricted diets would comprise symptomatic treatment, destined to fail over the long term for most people in an environment of unlimited food availability. Such diets could exacerbate the underlying metabolic dysfunction by further limiting metabolic fuel availability, lowering energy expenditure, and increasing hunger (recapturing the starvation response amid apparent nutritional adequacy). However, qualitative aspects of diet may improve metabolic function and increase

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circulating concentrations of metabolic fuels independent of calorie content. One approach aims to reduce insulin secretion with a low glycemnic index or a low-carbohydrate diet. In support of this possibility, energy expenditure was about 325 kcal/d greater while consuming an isocaloric low carbohydrate (60% fat) vs conventional (20% fat) diet in a controlled feeding study of weight loss maintenance. Other dietary factors speculated to decrease anabolic drive include low refined sugar intake, high polyunsaturated to saturated fat ratio, high omega-3 and low trans-fatty acid intake, adequate protein, high micronutrient and phytochemical content, and probiotics and prebiotics. Physical activity level, sleep, and stress may also, directly or indirectly, influence calorie uptake and storage in the adipocyte.

Future Research Needs

Several large dietary counseling studies reported no difference in body weight between treatment groups differing in macronutrient composition. Although these studies demonstrate the challenges to lasting behavioral change in the modern food environment, the inherent efficacy of specific diets cannot be examined because of limited differentiation among treatment groups. For example, 811 participants in the Pounds Lost Study reported mean maximum differences of only 9% in dietary fat and 5% in protein across 4 treatment groups. Actual intakes may have differed by even smaller amounts because of the possibility of social desirability bias in self-reports. In contrast, clinical trials using partial food provision to enhance differentiation, such as in the DIRECT (Dietary Intervention Randomized Controlled Trial) study and Diogenes (Diet, Obesity, and Genes) Project, suggest important effects of dietary composition on body weight and metabolic outcomes.

Ultimately, weight loss requires consuming fewer calories than expended. A common interpretation of this thermodynamic principle de-emphasizes the importance of dietary composition and instead places focus on behavioral methods to establish a negative energy balance. Although reduced energy intake acutely decreases fat mass, predictable physiological and behavioral adaptations progressively lessen the ability of most people to maintain voluntary energy restriction. According to an alternative view, the metabolic effects of refined carbohydrate (consumed in greater amounts now than in the 1970s, with adoption of the low-fat diet) and other environmental factors cause the adipocyte to take in, store, and trap too many calories. Subsequently, energy expenditure declines and hunger increases, reflecting homeostatic responses to lowered circulating concentrations of glucose and other metabolic fuels. Thus, overeating may be secondary to diet-induced metabolic dysfunction in the development of some forms of obesity. If so, treatment focused on dietary quality, rather than advice to eat less, could help address this sequence of events at the source and produce better long-term weight loss. Mechanistically oriented trials with well-differentiated diet groups and comparative effectiveness studies addressing this controversy are under way.

ARTICLE INFORMATION
Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and no relevant conflicts were reported.
Additional Contributions: We thank: Jeffrey S. Flier, MD, Harvard Medical School; C. Ron Kahn, MD, Joslin Diabetes Center; and Joseph A. Majzoub, MD, and Cara B. Ebbeling, PhD, Boston Children’s Hospital for critical review of an earlier version of this manuscript. None of these individuals received compensation for their efforts.
Correction: This article was corrected on May 21, 2014, to fix a typographical error and to add an existing reference to support a point.

REFERENCES