Obesity Pathogenesis: An Endocrine Society Scientific Statement

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ABSTRACT Obesity is among the most common and costly chronic disorders worldwide. Estimates suggest that in the United States obesity affects one-third of adults, accounts for up to one-third of total mortality, is concentrated among lower income groups, and increasingly affects children as well as adults. A lack of effective options for long-term weight reduction magnifies the enormity of this problem; individuals who successfully complete behavioral and dietary weight-loss programs eventually regain most of the lost weight. We included evidence from basic science, clinical, and epidemiological literature to assess current knowledge regarding mechanisms underlying excess body-fat accumulation, the biological defense of excess fat mass, and the tendency for lost weight to be regained. A major area of emphasis is the science of energy homeostasis, the biological process that maintains weight stability by actively matching energy intake to energy expenditure over time. Growing evidence suggests that obesity is a disorder of the energy homeostasis system, rather than simply arising from the passive accumulation of excess weight. We need to elucidate the mechanisms underlying this "upward setting" or "resetting" of the defended level of body-fat mass, whether inherited or acquired. The ongoing study of how genetic, developmental, and environmental forces affect the energy homeostasis system will help us better understand these mechanisms and are therefore a major focus of this statement. The scientific goal is to elucidate obesity pathogenesis so as to better inform treatment, public policy, advocacy, and awareness of obesity in ways that ultimately diminish its public health and economic consequences. ***(Endocrine Reviews 38: 267 – 296, 2017)***

ISSN Print: 0163-769X
ISSN Online: 1945-7189
Printed: in USA

Received: 11 May 2017
Accepted: 12 May 2017
First Published Online: 26 June 2017

Stratification of obesity outcomes
Unraveling mechanisms linking the environment to defense of elevated body weight
Identifying and mitigating environmental risk factors
Translating basic science into more effective pharmacotherapy

ESSENTIAL POINTS

- Obesity pathogenesis involves two related but distinct processes: (1) sustained positive energy balance (energy intake > energy expenditure) and (2) resetting of the body weight "set point" at an increased value. The latter process explains why weight lost through changes of diet and/or lifestyle tends to be regained over time, a major obstacle to effective obesity treatment.
- How the increased body weight comes to be biologically defended remains uncertain, although ongoing research is beginning to shed some light on underlying mechanisms. Therapeutic strategies that target these mechanisms have the potential to reset the defended level of body weight at a lower, more normal value.
- The impact of diet on obesity risk is explained largely by its effect on calorie intake, rather than by changes of either energy expenditure or the internal metabolic environment. Stated differently, "a calorie is a calorie." Thus, habitual consumption of highly palatable and energy-dense diets predispose to excess weight gain irrespective of macronutrient content.
- Beyond diet, environmental factors ranging from socioeconomic status to chemical exposures to sedentary lifestyle can confer obesity risk. How these inputs interact with genetic, epigenetic and developmental factors that predispose to obesity is a key question for future research.

The need to integrate molecular, genetic, developmental, behavioral, and environmental factors highlights the substantial challenge inherent in achieving a comprehensive understanding of obesity pathogenesis. Mechanistic formulations must draw from disciplines that include: the neuroscience of feeding behavior; the psychology of food reward; the metabolic impact of specific nutrients and changes of physical activity; as well as genetics, epigenetics, and developmental biology relevant to energy balance control, and the influence of exposure to environmental variables ranging from endocrine-disrupting chemicals (EDCs) to socioeconomic factors. When processing this information, one must also be mindful that although there are many interventions that can cause obesity in an experimental setting, the key question is whether they do cause obesity in a naturalistic environment. In this statement, we focus on factors for which compelling evidence exists that implicates them in the pathogenesis of either the accumulation or maintenance of excess body fat mass.

Definition

Obesity is broadly defined as an excess of body-fat mass. Reliable fat-mass quantitation requires sophisticated tools that are not widely available (*e.g.*, magnetic resonance imaging or dual energy X-ray absorptiometry), and this has hampered efforts to arrive at a more specific definition. Consequently, an elevated body mass index (BMI), which expresses body weight (in kilograms) as a function of body height (in meters^2) as a surrogate measure of body fatness, is the most widely accepted definition of obesity. Population-based actuarial studies place the upper limit of normal BMI in adults at 25 kg/m^2, define obesity as a BMI > 30 kg/m^2, and designate a BMI between these values to be "overweight." The degree of obesity can be further subcategorized into class 1 (BMI of 30 to <35), class 2 (BMI of 35 to <40), and class 3 (BMI of >40) (1). Assessing BMI in children requires adjusting for both age and gender.

BMI satisfies our need to estimate body-fat mass at a population level and thus gauge a group's susceptibility to complications of obesity. However, it is not a reliable clinical tool for assessing individual body fatness, because variations in skeletal muscle and other lean-body-mass components create substantial variations in total body mass. For example, a heavily muscled individual with increased body weight relative to height will have a BMI value that can erroneously place them into the overweight or even obese category. Additionally, there are significant racial/ethnic differences in how BMI associates with adverse medical consequences. (For additional information, see the companion Endocrine Society Scientific Statement titled "Obesity Management: Past, Present, and Future; Science and State of the Art.")

Rationale for a scientific statement on obesity pathogenesis

For most endocrine disease, researchers have established effective therapeutic treatments based on underlying disease mechanisms. This is not the case with obesity; unlike most other endocrine disorders, we have a very limited understanding of its pathogenesis, despite decades of research and billions of dollars spent each year on its treatment. This gross expenditure of time and money is undoubtedly linked to the extraordinarily high prevalence (affecting one-third of the adult United States population) (2), ease of detection, and stigma associated with obesity. These factors conspire to create an enormous demand for weight-loss products and services that continue to

flourish, despite being largely ineffective, sometimes dangerous, and almost entirely unregulated (3).

This situation is not unlike the medical practice of a century ago in which "glandular extracts" were cleverly marketed for a multitude of diseases, generating robust sales and profits for their manufacturers despite a lack of efficacy or safety data (4, 5). It was largely in response to the rise of this practice (termed "organotherapy") that the Endocrine Society chose a different path. In the third year of its existence, the Endocrine Society elected Sir Harvey Cushing as President. In his presidential address, he advocated strongly in favor of adopting the scientific method and abandoning empiricism to better inform the diagnosis and treatment of endocrine disease (6). In doing so, Cushing helped to usher in the modern era of endocrinology and with it, the end of organotherapy. (In an interesting historical footnote, Cushing's presidential address was given in 1922, the same year that insulin was discovered.)

Clearly, we need a well-defined, generally accepted set of physiological, developmental, and environmental principles regarding body weight homeostasis that will inform strong research and therapeutic strategies regarding obesity pathogenesis. The current lack of consensus regarding obesity pathogenesis has resulted in competing and poorly justified claims both from within and outside of the scientific community. These inconsistencies erode public trust and confidence in the scientific process as it pertains to obesity and its treatment, which only further supports nonscientific ideologies and products. To break this vicious cycle, and to identify effective treatments, we need to establish clearly defined and reliable data regarding obesity's underlying causes.

Energy Homeostasis and the Physiological Control of Body-Fat Stores

General principles

Background

At its most basic level, the pathogenesis of obesity seems simple: Calories are consumed in amounts that exceed ongoing energy expenditure. Based largely on this concept, most people have historically perceived obesity as the result of negative personal traits, such as gluttony, sloth, self-indulgence, laziness, and lack of will power. However, growing evidence indicates that obesity pathogenesis involves processes far more complex than the passive accumulation of excess calories. It is this complexity that lies at the heart of why obesity is so difficult to treat. Fundamentally, humans have an "evolutionary physiology" that is predisposed to conserve body fat as a factor of survival. This evolutionary physiology in today's climate of easy access to virtually unlimited calories has created a large segment of humanity that appears to be biologically predisposed to excessive weight gain. Hence, we see upward trends of adiposity in developed and developing communities.

How does the energy homeostasis system bear on this issue? We see clear evidence of a properly operating energy homeostasis system in the remarkable body-weight stability of individuals who are not obese over long periods of time. Evidence from an observational study of 15,624 healthy Swedish women (7) indicates that participants were, on average, >99.5% accurate in their annual matching of energy intake to expenditure for 10 consecutive years of observation. To better understand the implications of this observation, consider that a healthy adult weighing 165 pounds can be expected to gain >2.2 pounds in a year if they expend 27 fewer calories per day than they consumed. During 50 years of adulthood [assuming a caloric intake of 2500 kcal/day (46.6 M kcal total)], a weight gain of 1 pound (~2270 kcal/pound mixed body tissue) per year (113,636 kcal total) is equivalent to a 0.24% positive caloric balance. Thus, we infer that such individuals are >99% accurate in matching energy intake to expenditure. There are caveats to such calculations relating to the fact that increased body mass increases energy expenditure (further reducing the balance error), but from a thermodynamic perspective, it is clear that obesity is generally the consequence of small, cumulative imbalances of energy intake and expenditure. Although the causes of these imbalances can involve innumerable genetic, developmental, and/or environmental factors, once individuals who are obese and individuals who were never obese achieve their "customary" body weights and compositions, they tend to maintain and defend those weights by identical mechanisms.

Studies investigating the adaptive responses of normal-weight humans and animals to changes in body weight support the concept of a physiologically important energy homeostasis system. Weight loss induced by caloric restriction, for example, results in both an increased drive to eat and a reduction of energy expenditure. These responses both resist further weight loss and favor recovery of lost weight, and they can persist for years, provided that body-fat stores have not returned to baseline (8). These adaptive responses to weight loss are reported in both individuals who are obese and lean individuals (9), therefore suggesting that obesity pathogenesis involves the physiological defense of a higher level of body fat. This perspective offers a plausible explanation for the very frequent regain of lost weight that confounds most forms of obesity treatment (10, 11).

Conversely, normal-weight subjects respond to experimental weight gain (induced by "forced overfeeding") by increasing energy expenditure and reduced hunger. Once forced overfeeding is discontinued, a combination of decreased drive to eat and increased energy expenditure tends to restore body weight to normal (9). Indeed, such overfeeding studies show that it is surprisingly difficult for normal-weight

individuals to achieve and sustain experimentally induced weight gain (12). Individuals who are obese also resist excess weight gain induced by forced overfeeding (13). Therefore, their elevated levels of body-fat mass appear to be similarly subject to biological defense. Stated differently, individuals who are obese and individuals who are not obese appear to use the same homeostatic mechanisms to defend different levels of body-fat mass. This observation suggests that dysfunction of the energy homeostasis system is both necessary and sufficient for the biological defense of elevated body weight in individuals who are obese (14). What remains unclear is how this dysfunction is linked to factors that enable excess weight gain, such that excess body-fat mass comes to be biologically defended. This issue is central to obesity pathogenesis and therefore a central focus of this scientific statement.

Leptin and energy homeostasis

The adipocyte hormone leptin, which circulates at concentrations proportional to body-fat mass, plays a significant role in the relationship between obesity and energy homeostasis. A deficiency of leptin causes severe hyperphagia and obesity in both humans and animals (15), with physiological leptin replacement ameliorating both the hyperphagia and obesity in leptin-deficient individuals (16). Therefore, there can be no question that normal body-weight maintenance in humans requires intact leptin-regulated neurocircuits.

However, these observations do not indicate that genetic deficiencies of leptin or its cognate receptor are important causes of human obesity. Although such individuals exist, they are rare (17). In contrast, most individuals who are obese have elevated plasma leptin levels (in proportion to the increase of body-fat content), raising the possibility that common forms of obesity are associated with "leptin resistance" (*i.e.*, that supraphysiological plasma leptin levels are required to overcome tissue resistance to leptin and thereby enable energy intake and energy expenditure to match one another). Because adipocytes secrete leptin in proportion to body-fat content, the only way to raise plasma leptin levels in this setting is to become obese.

These considerations would seem to point to a causal role for leptin resistance in the pathogenesis of common forms of obesity, but the matter remains unsettled. For one, there is no uniformly agreed-upon definition for leptin resistance (18), and the presence of hyperleptinemia *per se* cannot be taken as evidence of its presence. Indeed, recent data suggest that the cellular response to leptin (*e.g.*, activation of intracellular STAT3 signaling) is preserved in obese, hyperleptinemic rodents (19). The circulating leptin concentration needed to fully engage central nervous system responses likely differs among individuals based on the influence of genetics, development, and possibly diet. Thus, some individuals who are obese may simply require more leptin (and hence body fat) to fully engage relevant neurocircuits (20).

Given the evolutionary considerations alluded to above, the primary role played by leptin-responsive neurocircuits may be related more to preventing loss of body fat (communicated to the brain by a decrease of leptin signaling) than to defending against its increase (conveyed by increased leptin levels). In this formulation, genetics, development, and even environmental factors can influence the level of leptin signaling ("threshold") below which compensatory increases in food intake and reductions in energy expenditure occur. Accordingly, this theory holds that leptin circuitry is more sensitive to decreases than to increases in the circulating leptin level, with the limited response to leptin concentrations above the lower threshold offering a potential explanation for what some refer to as leptin resistance. The apparent resistance in this formulation is simply a reflection of the circuitry's design (20, 21). More work in this area is clearly needed.

Fuel partitioning, insulin, and obesity

General perspectives on obesity pathogenesis have swung from early conceptualizations of obesity as a storage disease of adipose tissue (analogized presumably to some of the earliest identified inborn errors of metabolism by Garrod) to more recent brain-centric models, in which the brain, by virtue of its operational control of food intake and energy expenditure, imposes excess calories on passive adipocytes. Sometimes referred to as "pull" and "push" models, respectively, each makes very different predictions regarding both underlying molecular mechanisms and how we should approach obesity prevention and treatment. Embedded within this debate is the extent to which adipocyte-autonomous processes can pull substrate molecules preferentially into adipocytes, and by "partitioning" calories in this way cause higher fractional deposition of calories as fat. A key prediction of this model is that some individuals who consume a diet in which caloric intake and energy expenditure are matched (*e.g.*, an isocaloric diet) will preferentially deposit ingested calories as fat at the expense of their lean tissue mass, thereby becoming relatively fatter without entering a state of positive energy balance *per se* (see the section titled "Impact of diet composition on obesity risk").

Although it is possible that variations in body composition among individuals of the same body weight reflect (to some extent) the consequences of such processes, achieving clinical obesity in this manner must be rare, because most individuals who are obese have absolute increases of both lean and fat mass. Nevertheless, when leptin-deficient *ob/ob* mice are pair-fed the same amount of food consumed by normal controls, they gain more mass (due to reduced energy expenditure) and preferentially deposit that mass as fat, leading to an absolute and relative deficiency of lean mass in these animals (22). Although the mechanism underlying this partitioning effect must relate to developmental and/or intercurrent effects of leptin (perhaps involving interactions with insulin as well), the precise biology is not clear (22). The hypothesis that leptin plays a direct role in these processes is supported by evidence of its direct effects on lipid partitioning in skeletal muscle (22).

Lipoprotein lipase (LPL), an enzyme that hydrolyzes circulating apolipoprotein-bound acylglycerides at the surface of many cell types (including adipocytes and myocytes), also appears to affect the partitioning of fatty acids in ways that affect both absolute and relative fat mass. Although mice overexpressing LPL in skeletal muscle accumulate triglyceride in muscle and are resistant to increases of adipose tissue mass during overfeeding (23), overexpression of LPL in adipocytes does not affect body weight or adiposity in mice (24). Restoration of muscle LPL in mice that otherwise lacks the enzyme creates animals functionally lacking LPL in adipose tissue; surprisingly, these mice are characterized by normal body-fat mass, apparently because of a compensatory increase of fatty acid synthesis in adipocytes (25). Expression of LPL varies widely by depot in humans, and it might account for differences in adipose tissue distribution in some individuals. As insulin increases the synthesis and activity of LPL (while also stimulating adipocyte uptake of fatty acids and glucose), intrinsic differences in insulin-mediated molecular processes could (in theory) play a determinative role in body-fat content and/or distribution. In this context, however, it is important to note that humans lacking LPL on a genetic basis have normal fat mass due to the ability of adipocytes and muscle to take up circulating free fatty acids in quantities sufficient to allow adequate aclyglyceride formation in adipose tissue or oxidation in muscle (26). Therefore, although local activity of LPL (in adipocytes and muscle) could play a role in partitioning of fat among tissues, it appears to be neither necessary nor sufficient for the uptake of fatty acids into adipose tissue.

Several investigators have proposed that the effect of specific diet components on insulin secretion or action contributes to obesity pathogenesis through effects on calorie deposition in adipocytes, rather than (or in addition to) effects on energy balance *per se*. Essentially, carbohydrates in general (and refined and possibly naturally occurring sugars in particular) are proposed to promote hyperinsulinemia that in turn drives glucose and fatty acids into adipose tissue (25). Accordingly, this process is proposed to cause obesity by both direct effects on adipocytes that favor fat deposition and by lowering circulating metabolic substrates (and/or exerting effects on hepatic metabolism) that subsequently stimulate food intake. Additional "lowering" effects on energy expenditure by these dietary components are proposed to exacerbate the tendency toward increased fat deposition (27). As we discuss in greater detail in a later section ("Diet composition, lifestyle, and obesity risk"), this hypothesis remains controversial and has yet to receive the level of support needed for broad acceptance. Among several concerns is that differences in diet composition have yet to be convincingly shown to cause differences in body composition when provided in an isocaloric manner (such that total calorie consumption is matched between diets) (28). This is not to say that diets high in refined carbohydrate and/or fructose (soft drinks) do not predispose to obesity, but the underlying mechanism is likely to involve excessive intake of calories, rather than nutrient-specific or hormonal effects on substrate partitioning.

Collectively, these data suggest that diet composition *per se* (relative quantities and specific types of carbohydrates, sugars, and fatty acids, as distinct from caloric content) contributes far less to the etiology of obesity than do contributions made by the net imbalance of intake and expenditure. It therefore follows that although variations in diet composition can powerfully affect palatability and hence hedonically motivated feeding, whether it can also influence food intake via secondary metabolic consequences (*e.g.*, effects of insulin on circulating nutrient levels) remains a highly controversial topic that seems unlikely to be resolved without clinical studies that will be costly and challenging to undertake.

Neurobiology of energy homeostasis

Background

More than 60 years ago, to account for evidence that body weight is biologically defended, Kennedy (29) proposed that body-fat mass is regulated by an "adiposity negative feedback" system. Specifically, he suggested that circulating signals inform the brain regarding the amount of body fuel stored in the form of fat. In response, the brain makes compensatory adjustments to both food intake and energy expenditure so as to promote weight stability. Compelling support for this hypothesis has emerged in the decades since, including the identification of neurocircuits and signaling molecules that sense, integrate, and transduce humoral input relevant to body-fuel stores into adaptive changes of energy balance. Because a credible formulation of obesity pathogenesis depends on a comprehensive understanding of how food intake and energy balance are controlled, we explore this topic in detail here.

Motivational aspects of feeding behavior provide a useful context within which to introduce the topic of energy balance neurocircuitry. Both "metabolic need" and "food reward" have long been considered key drivers of feeding. The former involves a desire to alleviate the discomfort associated with inadequate food availability ("drive reduction"), whereas the latter describes the anticipation of a rewarding experience and subsequent fulfillment of that experience (30). Recent advances in neuroscience have enabled the identification of neuronal substrates implicated in these distinct but complementary sources of motivation.

Hypothalamic neurons controlling energy balance

Perhaps the best studied subset of neurons involved in feeding behavior are those that co-express neuropeptide Y (NPY), agouti-related protein (AgRP) (an antagonist of melanocortin signaling), and the inhibitory

neurotransmitter, γ-aminobutyric acid (GABA); henceforth referred to as AgRP neurons, because they are the only neurons that express AgRP. Located in an area of the mediobasal hypothalamus known as the arcuate nucleus (ARC), AgRP neurons are activated in conditions of negative energy balance and weight loss (*e.g.*, fasting), in part because such conditions reduce plasma concentrations of leptin and insulin, hormones that tonically inhibit these neurons (31). Because this inhibitory input becomes quiescent during fasting, AgRP neurons are activated and increase the drive to eat.

What evidence causally links AgRP neuron activation to increased food intake? Thanks to recent advances in optogenetics and related neuroscience methods, researchers have been able to investigate responses triggered by the selective activation or inhibition of uniquely identified neuronal subsets in conscious, freely moving animals. This work has convincingly revealed the powerful hyperphagic response elicited by selective AgRP neuron activation (32). Combined with evidence that AgRP neurons are activated across a variety of states of metabolic need that drive hyperphagic feeding (*e.g.*, fasting, uncontrolled diabetes, genetic leptin deficiency, and hypoglycemia), researchers have suggested a causal role for their activation in the associated hyperphagia (33). This possibility received direct support following the demonstration that experimental silencing of AgRP neurons prevents hyperphagia elicited by fasting (32).

Recent work has identified several unique and unanticipated properties of AgRP neurons. Using cell type–specific *in vivo* calcium imaging in conscious, free-moving mice, Knight *et al.* (34) documented that although AgRP neurons are activated in fasted mice, as expected, they cease firing upon the sight of food, prior to feeding onset. Although originally interpreted to suggest that activation of AgRP neurons merely prepares animals to eat, rather than driving feeding behavior *per se*, the same group showed that if food is made available only after activation of AgRP neurons ceases, intake still increases markedly (as long as food is made available within 30 minutes) (35). Thus, activation of AgRP neurons provides a robust stimulus to feeding that continues throughout a meal, even though activity of these neurons ceases prior to meal onset.

Whether activation of these neurons increases intake by enhancing the rewarding properties of food or whether it motivates feeding through drive reduction (a desire to alleviate the discomfort associated with not eating) is an active and somewhat controversial area of study. Sternson *et al.* (36) suggested a key role for the latter mechanism, implying that AgRP neuron activation is aversive when food is not available, and that feeding ameliorates this effect. Conversely, Knight *et al.* (35) reported that as long as food is available, animals perceive AgRP neuron activation as being highly rewarding. Whether animals perceive AgRP neuron activation as a positive or a negative experience may therefore depend on whether food is available.

Situated adjacent to AgRP neurons in the ARC are neurons that express pro-opiomelanocortin (POMC) and release the anorexic neuropeptide α-melanocyte–stimulating hormone. Food intake is reduced following the activation of melanocortin 4 receptors expressed on "downstream" target neurons in the paraventricular hypothalamic nucleus and other brain areas, and leptin stimulates POMC neurons (37). In conditions of negative energy balance and leptin deficiency, therefore, POMC neurons are inhibited, whereas AgRP neurons are activated (33). This combination drives feeding in the same way that a car is propelled forward by stepping on the accelerator pedal (AgRP neuron activation) while also removing one's foot from the brake pedal (POMC neuron inactivation).

Just as leptin's ability to reduce food intake and body weight requires an intact melanocortin system, mutations that impair the melanocortin system cause hyperphagic obesity in both humans and rodent models (17). POMC neurons are also targets for the action of certain anorexic agents, including serotonergic drugs (38). Because the degree of hyperphagia and obesity induced by defective melanocortin signaling is greatly enhanced by consuming a highly palatable diet, the melanocortin system appears to play a physiological role to limit reward-based feeding (39). Additionally, a recent study reported that adjacent to AgRP and POMC neurons in the ARC is a distinct and previously unrecognized subset of excitatory neurons that, when activated, powerfully and rapidly inhibit feeding (40). How these neurons fit into the bigger picture of energy homeostasis will undoubtedly be the subject of intensive additional study.

A relevant consideration here is that food intake regulation involves distinct components operating across very different time periods. Some neurohumoral mechanisms exert very rapid effects of short duration (*e.g.*, a single meal), whereas others are more modest but sustained over long time intervals. Yet each is somehow integrated to enable the precise long-term constancy of body weight mentioned above, and each can respond in an integrated manner to perturbations of body weight, although not necessarily through reciprocal effects on the same processes.

Delineating the mechanisms responsible for this seamless integration is a critical issue for the future study of the biology of energy homeostasis. Related issues are how homeostatic and hedonic drivers of energy intake interact, how this interaction is woven into long-term control of energy balance, and whether defects in this integration contribute to obesity pathogenesis.

Hindbrain circuits and the parabrachial nucleus

Because experimental activation of POMC neurons is not associated with rapid or potent feeding inhibition, the melanocortin system does not appear to be important for meal termination under physiological conditions. The latter process involves meal-induced

secretion of gut-derived peptides, such as glucagon-like peptide 1 and cholecystokinin, that, following their release by enteroendocrine cells in the gastrointestinal (GI) tract, play a physiological role to promote satiety by activating an ascending visceral sensory circuit (41). This circuit originates with vagal afferent neurons that convey GI signals to hindbrain areas, including the nucleus of the solitary tract. Some of these hindbrain neurons project to the parabrachial nucleus, which is a central node in this ascending pathway. Of particular relevance are calcium gene-related peptide expressing neurons in the parabrachial nucleus ($CGRP^{PBN}$) neurons located within the external lateral subnucleus of the parabrachial nucleus. A variety of stimuli linked to food consumption activate these neurons, such as gastric distention, secretion of cholecystokinin, and glucagon-like peptide 1. Activation of $CGRP^{PBN}$ neurons is implicated not only in physiological satiety and normal meal termination, but also in anorexia elicited by a variety of aversive stimuli. Because hypothalamic AgRP neurons inhibit $CGRP^{PBN}$ neurons (42), activation of hypothalamic AgRP neurons appears to stimulate feeding, in part, by inhibiting $CGRP^{PBN}$ neurons.

Unlike what is seen with POMC neurons, experimental activation of $CGRP^{PBN}$ neurons causes anorexia that is rapid in onset, severe, and if sustained can lead to life-threatening weight loss (43). Conversely, inactivation of $CGRP^{PBN}$ neurons increases meal size and blocks the satiating effects of cholecystokinin and glucagon-like peptide 1, implicating these neurons as physiological mediators of meal termination (43). However, because the increase of meal size induced by $CGRP^{PBN}$ neuron inactivation is offset by a proportionate reduction in the number of meals, net food intake does not change. Therefore, normal energy homeostasis does not appear to require activation of these neurons, even though meal termination does (43). Unlike what is observed in mice with defective melanocortin signaling, $CGRP^{PBN}$ neuron inactivation also does not increase intake of a highly palatable diet, nor does it predispose to diet-induced obesity, whereas POMC neurons play a physiological role to limit food intake over long time intervals. Therefore, $CGRP^{PBN}$ neurons provide an immediate and powerful brake to food consumption during individual meals.

Importantly, note that although these observations highlight relevant recent advances in the neurobiology of feeding, the substantial complexity inherent in food intake regulation cannot be reduced to a small set of interacting neurocircuits, and much remains to be learned in this field. Adding to this complexity is evidence that some of these neurons can affect feeding in unexpected ways. For example, $CGRP^{PBN}$ neurons are implicated not only in the perception of satiety but also in the transmission of aversive experiences that can lead to fear conditioning and formation of threat memory (44). It therefore seems somewhat surprising that activation of these same neurons during a meal plays a key role in the physiological experience of satiety. Despite its inherent complexity, further research in this area could lead to novel therapeutic agents for obesity.

Developmental considerations

Identifying the contribution of developmental influences to obesity risk is a daunting challenge because, as noted above, neurons regulating energy homeostasis are distributed throughout the brain (45, 46), and our understanding of the ontogeny and plasticity of these circuits is incomplete. Nevertheless, available evidence suggests that developmental influences can and do contribute to obesity pathogenesis in adults.

In rodents, circuits regulating distinct aspects of feeding behavior develop asynchronously. The most basic types of feeding regulation are present at birth, whereas the development of progressively more complex systems extends into adolescence. The capacity to regulate food intake in response to short-term signals associated with meal termination develops prior to the maturation of systems governing energy homeostasis. We can detect autonomic projections at birth that link rodent hypothalamus and brainstem to the stomach, and these projections continue to increase during the lactation period (45, 46). Food intake is suppressed in response to gastric distension as early as postnatal day 1, but it is not influenced by postabsorptive nutritional signals from the gut until postnatal day 9 to 11 (47, 48). Homeostatic feeding circuits that sense, integrate, and relay information about the availability of short- and long-term energy stores develop in the periweaning period (49–52). Projections from ARC neurons that convey nutritional (*e.g.*, glucose and fatty acids) and hormonal (*e.g.*, leptin and insulin) signals of energy status to preautonomic components of the feeding circuitry form in the third week of life (53), and responsiveness to adiposity signals (such as leptin) emerges 1 week after weaning (at 4 weeks of age) (50). Finally, processes that control motivated/rewarding aspects of feeding behavior are not established until postingestive consequences can be reinforced by the actions of corticolimbic circuits, which mature in the postweaning period (54, 55). Although the onset of corresponding regulatory networks has yet to be parsed in humans, individual patterns of food intake are apparently established between 1 and 4 years of age (56, 57). In both species, therefore, maturation of feeding circuits continues during the transition to independent feeding of solid foods.

Progress toward an understanding of developmental events regulating the maturation of feeding circuits is hampered by the fact that neurons with opposing effects on food intake are often interspersed within the same nucleus (58). Furthermore, neurons with similar peptidergic identities (*e.g.*, NPY, AgRP, GABA, and POMC) can respond differently to the same hormone and nutrient signals at different developmental stages (59), and they can also regulate feeding via projections to multiple downstream targets (60). The origin of ARC feeding circuits involves

progenitor cells in the basal aspect of the third ventricle that differentiate into immature postmitotic neurons at midgestation in rodents (61, 62) and by the end of the first month of gestation in primates (63). In mice, most of these immature ARC neurons initially express the *Pomc* gene (62), but during the course of gestation and early part of lactation, *Pomc* expression is gradually extinguished in many of these cells. As this occurs, these neurons begin to express the combination of neuropeptides and neurotransmitters that comprise the signaling outputs in the adult (*e.g.*, NPY, AgRP, and GABA). In AgRP neurons, this process occurs progressively, with expression of NPY turning on first, followed by GABA, and finally AgRP. Axonal outgrowth from ARC neurons to downstream targets begins at the end of the first postnatal week and is largely complete by the end of lactation in the third postnatal week (53). In nonhuman primates, in comparison, ARC projections develop during the third trimester of gestation (63), consistent with the fact that the lactation period in rodents corresponds developmentally to late gestation in humans (64). Consequently, many neurodevelopmental processes that occur *in utero* in humans do not take place until after birth in rodents.

Researchers have postulated a neurodevelopmental role for the surge of plasma leptin levels that occurs in rodents at the end of the first postnatal week (49). Although food intake is not sensitive to leptin at this age, developmental processes (such as axonal outgrowth) apparently are (65). Furthermore, during lactation, AgRP neurons (66) require leptin to project from the ARC to other areas, such as the paraventricular hypothalamic nucleus (65, 67). Following the transition to independent food intake at weaning, AgRP neurons begin to express adenosine triphosphate–sensitive potassium channels, which enable a switch in the response to leptin from excitation to inhibition (66). Presynaptic modulation of AgRP neuronal activity develops with the same temporal pattern as the postsynaptic systems outlined above, with excitatory inputs to AgRP becoming fully developed by the second postnatal week, whereas the number of inhibitory synapses increases after weaning. The onset of homeostatic regulation of feeding coincides with this final maturation step. These observations raise the possibility of a "developmental window" for the maturation of energy homeostasis neurocircuitry. We clearly need additional work in this area to further elucidate these developmental factors.

Signals relevant to the external nutritional environment (usually transmitted by the mother) can influence the maturation of ARC neurons. During gestation, for example, the metabolic status of the dam (*e.g.*, the presence of obesity-associated hyperinsulinemia) can influence the number of ARC neurons that adopt an anorexigenic POMC vs an orexigenic NPY cell fate (68), and during lactation, such influences appear to be magnified. For example, differences in the availability or composition of milk during lactation can affect the onset and the strength of the pup-derived leptin surge (69, 70). Exposure to maternal obesity or overnutrition during lactation can also reduce the number of neurons that express leptin receptors, with lasting impacts on leptin responsiveness (71, 72). Furthermore, the extent of axonal outgrowth from ARC neurons to their various target sites appears to be influenced by both milk-derived (insulin) and pup-derived (leptin) hormones (73, 74). Finally, if undernutrition sufficient to limit growth occurs during lactation, the maturation of systems that provide presynaptic (GABA) and postsynaptic (adenosine triphosphate–sensitive potassium channels) inhibitory signals to AgRP neurons is delayed (75). The existence of multiple steps at which ARC circuits can recalibrate to match the anticipated external environment likely underlies the extraordinary capacity of these circuits to compensate for early developmental deficits (76).

Although developmental influences on food intake regulatory circuits could certainly impact obesity susceptibility in adults, maternal programming of obesity susceptibility in rodents appears to arise more from reductions of resting (77) and activity-dependent energy expenditure (78) than from persistent effects on food intake (79). To better understand these effects, a brief focus on the ontogeny of autonomic nervous system neurocircuits regulating thermogenesis is warranted. The components of energy expenditure relevant to this discussion include heat produced either in the service of thermoregulation or in response to food consumption (diet-induced thermogenesis). The ontogeny of sympathetic circuits regulating nonshivering thermogenesis hinges on the coordinated development of both the nervous system and its target organ. In both neonatal rodents and humans, the primary means of heat generation is via activation of interscapular brown adipose tissue (iBAT) (80–82). In humans, the iBAT depot appears to be maximally active during infancy, before the development of systems that increase or decrease core body temperature by shivering or sweating, respectively. In rodents, iBAT remains the primary source of thermoregulatory heat production throughout the lifespan. This distinction between species is critical to interpreting how rodent studies relate to human physiology.

Whereas baselines of activity in feeding circuits are likely established by 3 to 4 weeks of age in rodents (83) and by 1 to 4 years of age in humans (84), circuits regulating resting energy expenditure (also referred to as basal metabolic rate) appear to mature later. For example, when a period of caloric restriction is imposed on obese mice between 3 and 5 weeks of age, the result is a paradoxical (and maladaptive) increase of resting energy expenditure (77), implying incomplete maturation of circuits controlling this response. Consistent with this observation, weight loss in young children who are obese is not necessarily followed by the compensatory decrease of circulating levels of free triiodothyronine (the active form of thyroid hormone that helps to determine basal metabolic rate) that

occurs in adults (85). Teenagers appear to be hypermetabolic compared with adults (86), potentially owing to higher endogenous brown/beige fat activity (87–89).

Unlike what occurs in rodents and other small animals, iBAT activity appears to decline with age in humans (81, 90, 91). Thermogenic circuits develop in several distinct phases (92). In both species, the iBAT depot is formed and produces key components of the thermogenic machinery (*e.g.*, uncoupling protein 1) during gestation, but it is not active until after birth. An immature phase of brown adipose tissue (BAT) thermogenesis is induced both by hormones released at parturition (*e.g.*, glucocorticoids and prolactin) and by factors released in response to the ketogenic diet of lactation (*e.g.*, FGF21) (82, 93). Hypothalamic neurocircuits that project to the brainstem and modulate sympathetic nervous system output regulate the mature phase of BAT thermogenesis; certain hormonal signals (*e.g.*, thyroid hormone) are also required. In rodents, both sympathetic projections and sympathetic nervous system–dependent stimulation of BAT activity develop during the suckling period (94–96).

Sensitive periods for development of circuits regulating BAT thermogenesis are distinct from those that characterize the development of ARC feeding-relevant circuits, in that neither maternal signals of metabolic status (97, 98) nor maternal environmental exposures (99) during gestation influence the formation of the iBAT depot or the expression of its associated thermogenic machinery. Nevertheless, leptin deficiency (67) or severe intrauterine growth retardation can cause diminished iBAT capacity in rodents (100), and leptin administration early in the postnatal period (postnatal days 4 to 12) can reverse these effects. Paradoxically, the same treatment leads to impaired BAT thermogenesis and increased susceptibility to diet-induced obesity when applied to wild-type mice nourished normally (69, 101).

Circuits regulating iBAT thermogenesis remain plastic throughout the weaning period. For example, weaning onto a high-fat diet (HFD) or during cold exposure leads to increased catecholaminergic innervation of iBAT (102, 103) with lasting impacts on thermogenic capacity and sensitivity to diet-induced obesity (103-105). Environmental programming of the maximal capacity of iBAT thermogenesis is correlated with lasting effects on the number of iBAT-innervating neurons in the sympathetic ganglia (103). In addition to upstream regulation of processes controlling sympathetic innervation, iBAT activation itself may alter the expression of neurotrophic factors that promote the outgrowth or survival of innervating sympathetic neurons. This notion is predicated on established evidence that signals from peripheral targets influence innervation by sensory nerves, and an analogous system operating in thermogenic circuits would provide a means of tuning neuronal outputs to match the anticipated need for iBAT thermogenesis.

Integrative physiology of energy homeostasis

Determinants of feeding behavior

In most mammals, food intake is organized into individual bouts (meals), the frequency and size of which can vary greatly to accommodate the needs of the organism. For example, predatory hunters, such as lions and wolves, may eat only every couple of days, provided that they can eat the entirety of their kill in what amounts to a single meal. In contrast, most humans eat multiple meals per day, and each meal constitutes a modest fraction of total daily caloric intake, with the number and size of meals per day ranging widely across populations and cultures. Ultimately, however, moment-to-moment regulation of intake serves the larger goal of maintaining adequate fuel stores to support life, and meal size and frequency can be adjusted so as to meet this goal (106).

The identification of neuromolecular mechanisms that integrate short-term and long-term control of feeding behavior, such that calorie intake precisely matches energy expenditure over long time intervals, will almost certainly enable better preventive and therapeutic approaches to obesity. The origins of the flexibility in meal size and frequency that serve this goal can be traced to differences in the biological underpinnings of meal initiation and meal cessation. Specifically, although researchers have proposed that changes in the internal milieu trigger meal initiation (*e.g.*, a decrease in circulating levels of glucose or an increase of plasma ghrelin levels) (107–109), the decision to begin a meal is also strongly impacted by a wide range of external variables, including food availability and palatability, the cost and risk associated with acquiring food (*e.g.*, threats from predators), and so forth.

In contrast to the considerable flexibility inherent in meal onset, meal termination appears to be highly regulated by postingestive feedback signals and other physiological variables. Accordingly, meal size is greatly increased when postingestive feedback is minimized, such as draining ingested food from the stomach (110). One implication of this observation is that meal initiation and its associated consequences (*e.g.*, activation of oral taste receptors) are themselves insufficient to elicit meal termination. However, available evidence points to a host of afferent humoral and neural signals arising from the interaction of food with the GI tract as primary determinants of the size of individual meals (see the earlier section titled "Hindbrain circuits and the parabrachial nucleus"). Both the time since the last meal and the status of intercurrent fat stores in the body can strongly influence the capacity of these physiologic signals to terminate a meal. Consequently, when energy stores (and therefore leptin levels) are low, these physiologic "satiety signals" are less capable of terminating a meal, thereby resulting in larger meal size (111). Such interactions among signals arising from the GI tract and those generated in proportion to stored fuel adjust ingestive behavior on a meal-to-meal basis, so as to

maintain stable body-fat stores. This process is fundamental to energy homeostasis, although it is incompletely understood.

Beyond this physiological control system, variations in both the type and amount of food available and the environment in which it is eaten can alter how much food is consumed at a single meal. For example, delivery of the same food in the same form repeatedly can reduce consumption, a phenomenon known as "sensory-specific satiety" (112). A more variable presentation of the same food can reverse this effect, even though overall diet composition is unaffected. Even factors such as the size of one's plate, the type of serving utensils, and the number of people in the room can influence the number of calories consumed in a single meal (113). What has been harder to determine is the extent to which such factors contribute to sustained alteration of overall energy balance. Although meal-size variation does not by itself appear to have much impact on body weight (because changes in meal frequency can compensate for this to maintain stable caloric intake), few studies have investigated the long-term consequences of changing meal sizes. Ongoing investigation into the effects of restricted feeding and intermittent fasting paradigms may prove interesting in this regard.

Determinants of energy expenditure

As noted earlier, in free-living adults, energy intake and expenditure are tightly coupled over long time intervals. A mismatch between intake and expenditure of as little as 3% can result in involuntary changes of body weight amounting to several pounds per annum, which (over time) could result in profound obesity. As weight increases, so does total energy expenditure. Consequently, total energy intake must increase gradually over time for a fixed caloric excess to persist. Although energy intake adjusts well to increased energy expenditure, this compensation appears to be less accurate at low levels of energy expenditure, favoring weight gain in sedentary individuals (114). Similarly, energy expenditure can compensate for a change of energy intake, although the "coupling" may be stronger when weight is reduced vs when it is increased. Therefore, whereas weight loss resulting from reduced caloric intake is strongly resisted by decreases of energy expenditure (both during and after weight loss), increases of energy expenditure induced by overfeeding tend to be more modest and short-lived (113).

Although the mechanisms underlying these responses (and the metabolic/endocrine connections linking intake and expenditure) are of major clinical importance, they are incompletely understood. In sedentary individuals, the following factors are the primary determinants of energy expenditure: cardiorespiratory activity and the maintenance of cellular ion gradients (resting energy expenditure, 60%); the digestion and initial distribution of food substrates (5%); and both planned or voluntary activity and low-level unplanned physical activity, including fidgeting (nonresting energy expenditure, 35%). Overfeeding raises energy expenditure in each of these compartments (due in part due to increases of both thyroid hormone levels and sympathetic autonomic activity); conversely, weight loss due to imposed caloric restriction reduces energy expenditure in each compartment.

Net gain in stored energy cannot occur unless energy intake exceeds expenditure. Cell-autonomous characteristics of adipocytes and skeletal myocytes, the chemical composition of the ingested calories, and the hormonal responses to these factors may (in theory) influence the chemical composition of stored energy (fat or lean mass). Although a low rate of resting energy expenditure predicts subsequent weight gain in some studies (115), and despite growing interest in the contribution made by brown and beige adipose tissue to energy expenditure in humans (116), the major cause of the energy imbalance implicated in the current obesity epidemic is excessive food intake (relative to energy expenditure) in the context of sedentary lifestyles. It would be interesting to identify the different contributions that autonomic activity, the thyroid axis, and brown/beige adipocytes make to resting energy expenditure in individuals who are preobese. However, it is unlikely that such differences (if they exist) will account for a substantial amount of risk variance in comparison with physical activity (for example). Furthermore, variations in energy intake (driven by a complex mix of endogenous and exogenous factors described earlier) typically have a much larger effect than variations in energy expenditure on overall energy balance. Another consideration is that therapeutic interventions that raise energy expenditure sufficiently to cause weight loss eventually trigger increased food intake as a compensatory response. For these reasons, the ability to influence and clinically manipulate energy intake is the more pressing goal where obesity treatment is concerned.

Mechanisms of Obesity Pathogenesis

Genetic factors: evidence for and against

Concordance rates for obesity in studies of both twin pairs and in adopted children suggest that 25% to 50% of the risk for obesity is heritable (117). Reasonable arguments can be made on evolutionary grounds that the current *Homo sapiens* genome is enriched for "thrifty" alleles that conserve calories and resist downward perturbations of weight that would—by virtue of effects on fat mass—impair reproductive efficiency (118). Others have argued that "predation release" (the reduced threat of predation brought on by advances in social behavior, weapons, and the use of fire) enabled more obese and therefore less agile hominids to escape predation, leading to changes in population adiposity as a result of random mutations and genetic drift (119). These are not mutually exclusive formulations.

The search for the genetic basis of the apparent "lipostat" for body fat led ultimately to the molecular

cloning of the *ob* and *db* mutations (in genes encoding leptin and the leptin receptor, respectively). These in turn led to the identification of a canonical molecular/cellular signaling pathway: LEP → LEPR → POMC, AgRP → PC1 → MC4R.

With the exception of MC4R, obesity-causing coding mutations in these genes are rare in humans. During the past 2 decades, genome-wide association studies (GWASs) and exome/genome sequencing studies have identified a large number of gene variants associated with more prevalent instances of obesity. It is disappointing that these strategies have been able to account for only a small fraction (~3% to 5% of interindividual variation) of the implied genetic risk variance for obesity. Sample size has been an issue with most candidate gene studies, but for some genes (*e.g.*, MC4R, ADRB3, BDNF, and PC1) the association studies are convincing, especially because hypomorphic alleles of each of these genes cause obesity in mice.

Since 2005, GWASs of obesity have tested associations of millions of relatively common (>5%) single nucleotide polymorphisms spaced more or less evenly across the genome with obesity-related phenotypes such as BMI, body-fat content, waist/hip ratio, response to bariatric surgery, and other phenotypes. Most of the subjects in these studies have been white adults. However, some studies included African Americans, East Asians, and children, and associations present in one adult population were generally present in others, as well as in children.

GWASs have identified many loci of small effect size. Importantly, note that single nucleotide polymorphisms themselves simply implicate a genetic interval and do not necessarily identify the relevant gene or allele, even if the single nucleotide polymorphism is within the coding region of a gene. This point aside, many of the ~100 GWAS-implicated loci for obesity (120) are preferentially expressed in brain, consistent with the large amount of research supporting primacy of the central nervous system in the control of energy homeostasis. Loci associated with body-fat distribution, in comparison, primarily mark genes implicated in adipose tissue biology.

The weak explanatory/predictive power of the alleles implicated by GWASs in obesity has led to the suggestion that other (as yet undiscovered) alleles (genetic "dark matter") exist that are of much lower frequency and higher phenotypic impact. Sequencing of the entire exomes of individuals has the potential to address this possibility. An alternative explanation is that individual risk alleles do not act in isolation. Rather, it is the interaction among different risk alleles or between these alleles and environmental factors that results in increased obesity risk. Quantifying these interactions, however, is a far more daunting challenge (requiring much larger sample sizes) that has yet to be met effectively (121).

Another area that has yet to be explored (mostly due to difficulties finding suitable subjects) is whether alleles of genes that protect against obesity exist and can be identified. Such genes/alleles would, presumably, be residue of earlier selection for phenotypes enabling predation avoidance, as we alluded to above. To the extent that these are hypomorphic alleles, the genes could provide attractive targets for inactivating drugs.

Interactions between genes, development, and environment

Although genetic factors acting in isolation are unlikely to explain the rapid increase of obesity prevalence during the past 40 years, it remains quite possible that certain genetic factors enhance the risk of obesity conferred by environmental influences in ways that favor positive energy balance (higher calorie intake, less physical activity, or both) and/or result in the biological defense of increased fat mass. The long list of potentially relevant environmental factors includes changes of diet composition and lifestyle, environmental toxins, infections, changes in the microbiome, and many others as well. Superimposed on these influences are the potential roles played by maternal obesity and diabetes. As discussed in the next section, the mechanisms responsible for transmitting such effects range from changes in maternal substrate provision and endocrine factors to effects conveyed by placental secretions into fetal circulation and effects on milk provided during lactation. Vertical "transmission" of phenotype in this fashion could exacerbate (or mitigate) shared genetic predispositions between mother and offspring while also affecting the phenotypes of progeny in the absence of primary genetic predisposition. Factors such as these almost certainly confound some of the efforts to quantify genetic risk for obesity and diabetes.

An example of interactions of genetic predisposition and lifestyle characteristics that influence obesity risk can be found in how levels of physical activity and diet composition strongly influence the impact of obesity risk alleles of the *FTO* gene (which encodes "fat mass and obesity-associated protein") (122). Additionally, single base pair sequence variations in noncoding portions of the first intron of the *FTO* gene have the strongest association with obesity in human populations yet detected (123). The effect size is not large, but the susceptibility alleles are very frequent in the population. There are apparently several mechanisms by which these noncoding variants affect obesity risk, mediated by effects on neighboring genes that influence brain development and/or function, as well as the development of beige adipose tissue (124).

Much of the sequence variation contributing to obesity risk will also likely be found in noncoding portions of the genome. Unfortunately, our grasp of the molecular genetics of noncoding DNA sequence variation (including epigenetic influences conveyed by these sequences) is insufficient for a clear understanding of how these factors might relate to human disease susceptibility.

Related to this issue and to the future identification of obesity therapeutics is an apparent conceptual bias

regarding the biological consequences of sequence variants implicated in these studies. The canonical pathway identified above relates primarily to secreted peptides/neurotransmitters and their cognate receptors. Even though interruptions of signaling can cause acute changes of energy expenditure and intake, these pathways also affect hypothalamic structure/connectivity both during development and in postnatal life (49). Thus, the consequences of congenital or acquired disruption may be long-lived. A potentially important example of a complex structure/pathway exemplifying a likely combination of such effects is the primary cilium of hypothalamic and other neurons that conveys both acute signaling and structural guidance in the development of circuits affecting food intake (125, 126).

These considerations highlight the possibility that genes that contribute to obesity susceptibility through direct effects on energy intake and expenditure may also influence the response to developmental/environmental factors, such as intrauterine and perinatal exposures to "obesogenic" diets, toxins, and others. By such mechanisms, genes/alleles not implicated in responses to earlier evolutionary factors might be implicated in responses to historically recent and novel factors. Future research regarding genetic and environmental/developmental factors that affect obesity will need to consider these pathways and mechanisms.

Role of epigenetic modifications

Epigenetic modification of genes typically involves changes in how transcriptional complexes access regulatory elements in the genome and can occur during development and throughout life. That substrates of intermediary metabolism convey some epigenetic modifications implies a sensitivity to nutritional status (127). Although examples exist in which developmental methylation changes are tied directly to obesity pathogenesis (128, 129), such effects are the exception rather than the rule. Epigenetic changes can program phenotypes in adulthood by affecting placental function, fetal growth rate, organ function, and the expression of metastable or imprinted genes involved in energy balance regulation.

At fertilization, there is a near-global resetting of the epigenome that accompanies the process of cellular differentiation from totipotent progenitors to specific cell identities that is mandatory for cell type specification (130). MicroRNAs also play a role in reinforcing cell fate decisions that progressively restrict the potential cell fates of progenitor cells. One form of epigenetic modification involves methylation of CpG sites that are established during development, and these can be inherited via semiconservative replication in progenitor cells. Once established, they are highly stable in differentiated cells (131). Some of these early methylation events occur on metastable alleles or imprinted genes, which can impart a lasting impact on numerous tissues, whereas others are restricted to specific cell lineages.

That maternal undernutrition increases obesity risk only during the first trimester is consistent with a role for early epigenetic processes (132). Methyl donor supplementation during rodent gestation can reverse adverse metabolic consequences programmed by undernutrition (133, 134), and methylation status in the periconception period is particularly sensitive to undernutrition. This is because high levels of homocysteine (due to folate deficiency) suppress the expression of DNA methylase 1 (a key enzyme for maintaining methylation during mitosis) (135), and supplementation with either folic acid or methyl donors during gestation can reverse these effects (128, 135, 136). Studies in both sheep and humans have reported hypomethylation of imprinted genes (*IGF2*) and metastable alleles (*POMC*) when the subject is severely undernourished early in gestation, but not when undernourished only in late gestation (137–139). Although early influences on the epigenetic modification of metastable or imprinted alleles can persist to adulthood, these changes do not correlate with later obesity risk within groups of similarly exposed individuals (137, 138, 140). Genome-wide epigenomic analysis of children of underweight mothers has identified thousands of hypomethylated loci (134), and some EDCs can induce hypomethylation that is reversible with maternal methyl donor supplementation (141). Future studies that clarify whether global hypomethylation results from impaired placental function or nutrient transport may help to explain why so many different maternal exposures yield overlapping phenotypic outcomes.

Although studies have reported associations between adult obesity and methylation marks on candidate loci in either cord blood or peripheral blood (134, 142–145), these findings are often either discordant with one another or inconsistent with differentially methylated loci identified in a genome-wide screen (or both). Impacts of maternal obesity may therefore be conveyed via tissue-specific mechanisms that cannot be assessed in the analyses of global methylation patterns in blood samples.

In some brain regions, as well as peripheral tissues (such as skeletal muscle and BAT), site-specific demethylation/remethylation driven by transcriptional or neuronal activity reorganizes the methylome (146–148). In tissues in which this remodeling is relatively restricted to the postnatal period, epigenetic marks reflective of the postnatal environment can persist to adulthood (147). For example, studies of several animal models of maternal overnutrition/obesity reported CpG hypermethylation and increased repressive histone marks on the *Pomc* locus, which persist to adulthood (149–152). These observations are consistent with the idea that epigenetic marks on the *Pomc* promoter underlie alterations in hypothalamic feeding circuits that diminish leptin responsiveness and consequently predispose not only to weight gain but to biological defense of elevated body weight. However, some studies involving maternal HFD feeding reported hypomethylation of the *Pomc* locus,

as well as dopamine- and opioid-related genes (153, 154). Even if we can potentially explain these differences via complex interactions between the effects of maternal nutrition on early methylation patterns and the later influences of the postnatal and postweaning environments on the remodeling of these epigenetic marks (150, 152, 155), they nevertheless challenge the reliability of epigenetic marks as a biomarker of future obesity risk.

Exposure to maternal obesity during gestation is associated with both an increased risk of obesity in offspring and decreased methylation of a developmental gene (*Znf483*) that promotes adipocyte differentiation (156–158). As this effect is associated with enhanced adipogenic potential of white adipose tissue (156–158), it could conceivably contribute to subsequent obesity risk. Although some early epigenetic marks are retained in adipose tissue, the adipose tissue methylome is sensitive to changes in diet, exercise, and weight loss throughout life (159–161), perhaps owing to the many different cell types represented in adipose tissue.

Collectively, this evidence supports the possibility of a causal link between the stable transmission of epigenetic marks, parental nutritional status in the periconception period, and programming of subsequent obesity risk. However, this hypothesis has very limited experimental support and hence only modest potential to explain the complex biology observed either in the laboratory or in human populations. Going forward, promising avenues of research include interdisciplinary approaches that combine epigenetic and developmental approaches to clarify how specific epigenetic changes influence overall fetal growth and tissue-specific developmental processes. Such studies are needed to delineate whether these processes contribute to the impact of maternal undernutrition or overnutrition on obesity risk in offspring.

Developmental factors: evidence for and against

During sensitive periods of development, ontogenic processes in both brain and peripheral organs can be modified so as to match anticipated environmental conditions. Although many exposures during development could potentially predispose to obesity in adulthood, we focus here on two that some researchers think contribute to the secular trends in obesity: parental obesity and exposure to EDCs.

Roles of parental body weight or diet

Undernutrition. The impact of developmental exposure to reduced maternal food availability has been examined both in animals and in human populations around the globe (162). Although these studies often report sustained effects on obesity risk, outcomes tend to be somewhat variable and sensitive to both the timing of developmental exposure and the relative abundance of food in the postnatal environment. Specifically, early gestational exposure to undernutrition followed by an abundant food supply in the postnatal period is reliably associated with an increased risk of obesity (132, 163, 164), whereas exposure late in gestation or the persistence of limited nutrient availability after birth is often protective against obesity. These observations are consistent with the theory that the undernourished fetus experiences changes in the energy homeostasis system that are adaptive when limited nutrient availability persists, but become maladaptive in a nutrient-rich environment (165, 166). We have not yet identified the mechanism underlying such a proposed change.

The observation that some of the adverse consequences of exposure to gestational undernutrition can be reversed by treatment with leptin (100) or folic acid (133) during the neonatal (but not the peripubertal) period (167) supports the existence of discrete sensitive periods (referred to as "critical windows") during which influences on developmental processes can have a lasting impact on metabolic disease risk. Although the early postnatal period in rodents likely represents one such window, whether corresponding processes occur in humans is unclear, especially because many developmental processes that occur postnatally in rodents take place during late gestation in humans (167). Although epidemiological studies suggest that maternal undernutrition predisposes to obesity in offspring in humans (167), we need additional information to determine whether such a mechanism contributes to the increased prevalence of human obesity in recent decades, and, if so, whether there is a critical window during which the energy homeostasis system is impacted in ways that predispose to obesity in adulthood.

Overnutrition/obesity. Although parental obesity is associated with an increased obesity risk in offspring, parsing contributions made by developmental exposure vs genetic or environmental factors is a difficult challenge. Studies in a genetically relatively homogeneous population at high risk for obesity (Pima Indians) point to a link between exposure to maternal (but not paternal) diabetes during gestation and an earlier onset of obesity (168), whereas maternal weight loss due to bariatric surgery prevents the transmission of increased obesity risk (169). Combined with evidence that the strongest predictor of childhood obesity is pregravid maternal BMI (134, 170), these studies support the idea that an obese gestational environment programs susceptibility to obesity.

In rodents, exposure throughout gestation and lactation to maternal consumption of an obesogenic HFD is correlated with persistent increases of adiposity in offspring (171, 172). However, this effect appears to be explained by exposure specifically during lactation, which leads to increased adiposity, irrespective of whether offspring are weaned onto chow or an HFD (74, 172, 173). Because the lactation period in rodents corresponds developmentally to late gestation in humans, there are very few scenarios in which obesity in human parents would be limited to only early or late gestation. Thus, offspring will typically be exposed throughout development. Whether the amount or type of food consumed by the mother has

developmental consequences that predispose to obesity independently of maternal obesity *per se* awaits further study.

Modes of transmission. Although initial efforts to model developmental exposure were focused on maternal transmission to progeny (F1 generation), recent studies have also explored the possibility of both paternal (F1) and transgenerational (F2) transmission. Paternal obesity is reported to impair placental and fetal growth in mice (174), but consequences for adiposity in offspring are variable (175–177). Although paternal exposure to famine has been suggested to program increased adiposity in humans (178), the contribution of paternal BMI to later obesity risk in broad-based population studies is weaker than the maternal contribution (134, 170), as might be expected. Although transgenerational transmission of obesity in humans has been suggested—through the paternal lineage in a largely homogeneous population of humans (179) or inbred rodents (176)—such effects are difficult to quantify, owing to the influence of many other variables that are difficult to control for.

These data collectively support the notion that developmental exposure to either undernutrition or obesity can increase susceptibility to obesity in offspring, and that the timing of exposure strongly influences such effects. However, we need more evidence to conclude whether these developmental exposures have contributed to the increase of obesity prevalence in human populations in recent decades.

Role of EDCs

Numerous studies link exposure to EDCs to a variety of outcomes of potential relevance to obesity, including stimulation of adipogenesis and changes of insulin secretion, insulin sensitivity, and liver metabolism. A recent Endocrine Society Scientific Statement provides a comprehensive review on this topic (180). In many cases, however, the relevance of these findings to obesity pathogenesis *per se* remains uncertain. Our focus here is limited to evidence that specifically links EDC exposure to the accumulation and maintenance of excess body fat mass.

That the increase of human exposure to EDCs parallels the rise in obesity rates in the United States (181, 182) raises the possibility of a causal link between the two. Many of these chemicals are classified as EDCs based on their capacity to mimic or alter receptor signaling by endogenous hormones, including estrogen, testosterone, and thyroid hormone (183). Whereas some EDCs are chemically unstable [*e.g.*, bisphenol A (BPA) and pthalates], several are highly persistent in the environment and bioaccumulate. These include brominated flame retardants; polychlorinated biphenyls; organotins, such as tributyltin; organochlorine pesticides, such as dichlorodiphenyltrichloroethane; and perfluorinated chemicals (PFCs) (180, 184). Although most of the latter chemicals are currently banned from use (with the exception of flame retardants), low-level exposure is widespread in human populations (181).

Maternal exposure to ECDs usually occurs via ingestion of contaminated food or beverages, although contact with personal care items, plastics, or other products that contain these chemicals can also contribute. These chemicals can also be transmitted to the fetus across the placenta or to an infant via breast milk (185). Compared with adults, relative levels of exposure as a function of body weight are higher for fetuses and infants (186), and exposure to low, environmentally relevant levels can program lasting effects (181,187). Given that some EDCs can act directly on adipocytes to promote adipogenesis (188–190), the possibility that low levels of these chemicals might program increased susceptibility to obesity later in life has been raised (191).

The potential contribution to obesity risk of developmental exposure to EDCs has been extensively reviewed, including two scientific statements published by the Endocrine Society (the first in 2009 and the second in 2015) (180, 187), a workshop sponsored by National Toxicology Program of the National Institute of Environmental Health Sciences (192), and elsewhere in the scientific literature (184, 193, 194). Yet unlike the consensus that exists regarding maternal metabolic influences on obesity risk, links between EDC exposure and obesity risk are a focus of ongoing research, with many key questions remaining unanswered. A brief comparison of how concern about the impact of maternal influences vs EDC exposure on obesity risk first came to light, and how the two research areas developed thereafter, offers insight into the origins of some of this uncertainty.

Compelling support for the involvement of maternal influences in programming metabolic outcomes first emerged from epidemiological observations in humans. These observations led to the development of animal models that have largely recapitulated these observations across multiple species, thereby creating a foundation upon which underlying cellular mechanisms can be investigated (for examples see earlier sections on both epigenetics as well as developmental factors). In comparison, evidence of a link between EDC exposure and obesity risk began with *in vitro* effects on master regulators of adipogenesis. These observations generated justifiable concern regarding risk to human populations and hence led to a search for evidence of a causal link through epidemiological studies and animal-based research, with mixed results. To illustrate the challenges inherent in transitioning from *in vitro* studies to animal models that are surrogates for human exposure, we focus on two specific EDCs—PFCs and BPAs.

PFCs

PFCs are widely used to make products more resistant to stains, grease, and water. Because they break down in the environment very slowly, they tend to bioaccumulate and can therefore persist in human tissues for years (195). Some classes of PFCs can bind to and activate the nuclear receptors peroxisome proliferator–activated receptor α and/or peroxisome proliferator–activated

receptor γ (a master regulator of adipogenesis), effects that can promote adipocyte proliferation and differentiation (189, 190, 196). These chemicals also have the potential to alter the methylation status of peroxisome proliferator–activated receptor γ or its target genes in ways that promote (or retard) adipocyte differentiation (196, 197). Other evidence suggests that some PFCs can alter thyroid function (198), which can secondarily impact both adipocyte biology and energy balance. Finally, some PFCs increase glucocorticoid concentrations by inhibiting the degrading enzyme 11β-hydroxysteroid dehydrogenase 2 (199), which also has the potential to increase obesity risk.

Another relevant consideration is that, as noted earlier, obesity risk in adults appears to be increased by any intervention that results in a period of growth restriction in early development followed by subsequent catch-up growth. Relevant to this issue is that meta-analysis of 21 studies in rodents (200) and nine studies in humans (201) supports the hypothesis that developmental exposure to PFCs reduces fetal growth. In some cases, therefore, the obesogenic effects of PFCs may be secondary to nonspecific effects on fetal growth rather than involving direct effects (*e.g.*, on adipogenesis) that predispose to obesity later in life.

BPA

As BPA is used in the production of polycarbonate plastics and epoxy resins, the main exposure route in humans is via bottles, food-can linings, and food packaging. Maternal BPA is transported across the placenta, with significantly higher concentrations in male fetuses (186). Young children can also be exposed through human milk, as well as through bottle-feeding (186).

There is little question that, unlike PFCs, BPA directly promotes adipogenesis in a peroxisome proliferator–activated receptor γ-independent manner (202). Although such an effect cannot, in and of itself, be assumed to cause or predispose to obesity, other potentially obesogenic effects of BPA include activation of estrogen receptor α (203, 204) or increased glucocorticoid synthesis (through actions on 11β-hydroxysteroid dehydrogenase type 1) (205). BPA-induced estrogen receptor signaling is also associated with increased expression of histone-modifying enzymes that cause global increases in repressive epigenetic marks (H_3K_{27} trimethylation) (206, 207) and changes of mitochondrial metabolism resulting from altered DNA methylation (208). There is therefore little question as to whether BPA can have biologically relevant and potentially concerning effects *in vivo* as well as *in vitro*.

Where obesity pathogenesis is concerned, however, data from animal models of low-level BPA exposure have been inconsistent. Thus, whereas several studies reported increased postnatal growth in rodents exposed to low-dose BPA during development (209–212), others reported no differences (213–215) or even reduced postnatal growth rates (216,217). In 2008, a review of the existing literature sponsored by the National Toxicology Program identified methodological and statistical concerns that may contribute to these discrepancies (186) and raised awareness about the potential impact of differences in experimental design that include diets, sex, species, strain and dose, duration, and route of exposure (217). The same organization subsequently convened a follow-up workshop in 2011 to reassess the state of the field and highlighted both continuing inconsistencies in animal data and the need for better metrics of obesity (fat mass, adipose tissue cellularity, and response to an HFD challenge), rather than relying solely on body weight (192).

This workshop also recommended the need for comparable dose-response information across studies to address peculiarities in the observed relationship between BPA exposure and excessive weight gain. For example, lower BPA-exposure levels often produce more profound effects than are observed at higher levels (184, 218, 219), and the dose of BPA (50 μg/kg/d) associated with increased adiposity in rats (220) elicits reduced adiposity in mice (221, 222). Further complicating matters are sexually dimorphic effects of BPA exposure, with increased body weight and liver weight but unchanged adiposity in males, and decreased body weight, liver weight, and adiposity in females (223). Such effects may reflect actions of BPA on brown adipose tissue and physical activity, as well as on white adipose tissue adipogenesis (223).

Additional concerns pertain to the nonmonotonic dose relationship between effects of BPA on liver vs adipose tissue. Specifically, doses that promote adiposity typically have no effect on the liver, whereas doses that impact the liver can have opposite effects on adipose tissue mass (221, 222). Based on these considerations, the consequences of developmental exposure to any particular dose of BPA on growth trajectories, body weight, and fat mass would appear to be influenced by the sum of its various effects on a variety of tissues. Metabolic and physiological outcomes can be further influenced by changes of BPA exposure during gestation vs during lactation and/or bottle-feeding.

Efforts to extend these findings to the consequences of BPA exposure for human obesity risk have encountered similar inconsistencies. For example, whereas evidence from cross-sectional studies shows a link between urinary BPA concentrations and childhood adiposity (224–226), prospective studies have reported reduced growth at birth or at 2 years of age (with a stronger effect in girls than boys) (227, 228), increased adiposity (229), or no effect (194, 226). In comparison, a link between BPA exposure and behavioral disturbances in boys is a more consistent finding in prospective epidemiological studies (194). Such effects seem worthy of investigation independent of the impact of BPA exposure on obesity risk.

Modes of transmission of endocrine disrupting chemical effects

In rodents, maternal exposure to organotins and organochloride pesticides (dichlorodiphenyltrichloroethane and methyloxychlor) is linked to increased

obesity risk in the F3 generation (230–232), despite inconsistent effects on F1 offspring (233). These observations raise the possibility of effects transmitted via epigenetic changes in the germline and transgenerational transmission of exposure-specific epigenetic marks (232). Should this interpretation prove correct, a relevant consideration is that most rodent studies of transgenerational transmission involve intercrosses between offspring with the same developmental exposure, a condition that is less common in humans.

GI factors, bariatric surgery, and the microbiome

Insights from bariatric surgery

There is little question that bariatric surgical procedures can produce profound and long-lasting effects on body weight. Chief among these procedures are Roux-en-Y gastric bypass and vertical sleeve gastrectomy, each of which can produce profound and sustained weight loss that cannot be reliably achieved by other means (234). Although these effects have historically been attributed to either caloric restriction (converting the stomach into a small pouch) or malabsorption (the loss of calories in the feces), neither explanation can account for the aggregate effects of these procedures. Of particular relevance is that patients report being less (rather than more) hungry following these procedures, even in the face of pronounced weight loss. In comparison, weight loss due to restricted food access or to conditions causing GI malabsorption clearly increases hunger, suggesting that these bariatric procedures suppress appetite even in the face of greatly reduced energy stores—ordinarily, a potent stimulus to food intake.

Among plausible mechanisms underlying the unexpected effects of Roux-en-Y gastric bypass and vertical sleeve gastrectomy on appetite is the possibility that these procedures alter communication between the GI tract and energy homeostasis neurocircuits (referred to as the "gut–brain axis"). Researchers have suggested that signals that might contribute to these effects include: gastric hormones, such as ghrelin; intestinal hormones, such as glucagon-like peptide-1 and peptide tyrosine tyrosine; and alterations in the level and composition of bile acids and/or the intestinal microbiome (235). These various mechanisms are not mutually exclusive, and each may contribute to effects on food intake control that result from surgical alteration of the GI tract. The larger point is that we cannot attribute the effect of bariatric surgery on energy homeostasis to simple mechanical alterations of the physical capacity of the GI tract to ingest food or absorb nutrients. Rather, these bariatric surgeries appear to lower the defended level of body-fat mass, presumably through effects involving the gut–brain axis.

This conclusion is consistent with rodent studies in which animals subjected to bariatric surgery actively defend a lower body weight, even when this involves increasing food intake (236, 237). It is tempting to speculate that this reduction of the defended level of body-fat mass reflects a reversal of pathogenic processes that led to obesity in the first place. However, it is also possible that the original pathological processes are not themselves altered by bariatric procedures, and that, instead, a host of nonphysiological responses collectively serve to lower the defended level of body weight. In either case, it is evident that the response of the gut–brain axis to these procedures can powerfully impact not only food intake but also the homeostatic regulation of body-fat mass. Studies that clarify how this occurs are a high priority, as are studies to identify cell types in the gut that convey these effects to the brain and the role of the liver as a potential intermediary in these processes.

The gut microbiome and other GI factors

How might such information inform our understanding of obesity pathogenesis? The importance of GI signals in meal termination, the potent effects of bariatric surgery on some of these signals, and the large sustained reductions in body weight from bariatric surgery support the hypothesis that obesity pathogenesis involves changes in the secretion or response to GI signals related to the composition and quantity of food. Yet despite the large number of experiments measuring gut hormone responses to different types of nutrients in individuals who are obese vs lean, a clear role for GI factors has yet to emerge, owing to both biological variation inherent in these responses and issues related to study design that make it difficult to compare results across studies. Thus, one can find examples of differences in almost any gut hormone response between individuals who are obese vs lean that are contradicted by examples where there are no meaningful differences. That obesity risk alleles have yet to be directly linked to GI signals by GWAS also argues against a causal relationship between GI factors and obesity pathogenesis (120).

The composition of the ~3 pounds of gut bacteria in humans has also been linked to obesity risk (238). Alterations in diet can profoundly affect the composition of gut bacteria at multiple levels of the GI tract, and obesity itself may also affect the composition of gut bacteria.

In mouse studies, transferring bacteria into the GI tract of germ-free mice causes weight gain, and the effect is modestly greater when the source is an obese donor vs bacteria from a lean animal (239). These and similar observations raise the possibility that the "obese" microbiome is capable of harvesting more realizable calories from ingested food than is the lean microbiome. The problem with this explanation is that simply increasing the energy harvested from ingested foods should elicit compensatory adjustments elsewhere in the energy homeostasis system (*e.g.*, reduced energy intake or increased energy expenditure) that limit weight gain, as detailed above. An alternative possibility is that gut bacteria generate biological signals (such as butyrate and other short-chain fatty acids) that impact the energy homeostasis system, and

that the composition of gut bacteria influences the nature of these signals (239, 240).

Evidence linking specific gut microbiota to obesity falls well short of establishing a causal relationship. Indeed, a recent analysis of available literature was unable to identify a reliable bacterial composition difference between humans who are lean and humans who are obese across different studies and different populations (241). Furthermore, a recent clinical trial found no evidence of a change of energy balance or other metabolic alterations arising from long-term administration of antibiotics that profoundly impacted the gut microbiome (242). An additional concern is the reliance on germ-free mice as a mainstay of basic research in this area. These animals at baseline have a lean, hypermetabolic phenotype and are resistant to weight gain when exposed to a HFD; the mechanistic basis for this phenotype remains uncertain. Although these phenotypic features tend to normalize following fecal microbiome transfer, the body weight of the donor does not dramatically affect the outcome. This observation is consistent with fecal transfer experiments designed to supplement an organism's existing microbiome. Whether conducted in rodents or humans, the effect on body weight tends to be relatively small (243).

One other experimental limitation that impacts the link between obesity and the gut microbiome pertains to differences between the microbiome of the large intestine and that of the small intestine. Whereas the donated microbiome usually is almost exclusively from fecal (or sometimes cecal) samples, variations in the microbiome that affect energy balance by influencing signals from the GI tract are likely to involve organisms in the small intestine as well as those in the large intestine. These considerations highlight the many questions that must be answered before the impact of the microbiome on obesity pathogenesis and its role in future interventions for obesity prevention or treatment are understood.

Social and economic factors

There is little question that in the United States obesity rates are linked inversely to socioeconomic status (SES), especially among women (244–248). Deducing cause and effect is complicated by the difficulty inherent in controlling for numerous potentially confounding variables (*e.g.*, genetic or epigenetic factors and environmental exposures that impact development). The focus of this section, therefore, is not on whether obesity is caused by economic insecurity (which cannot be ascertained from the available evidence) but rather on the extent to which highly prevalent social, economic, and cultural conditions influence obesity risk. Once we identify factors that impart the greatest obesity risk, future studies can begin to investigate whether and how they impact the energy homeostasis system.

Unlike obesity statistics at the national or county levels, which can obscure social disparities, new geolocalization and mapping approaches (249–253) are able to track the patterns of social, racial, and residential segregation and their impact on body weight and health. At the census tract level, obesity prevalence rates can vary from 0.05 to 0.30, depending on where people live. Analyses that accounted for variations in residential property values, education, and incomes have accounted for 70% of the variance in census tract obesity rates in Seattle/King County (254). Such geolocalized data provide a clear link (although not necessarily causal) between social and economic factors and obesity risk at the level of individual neighborhoods (with the caveats noted above).

Disparities in the types and amounts of food consumed are obvious candidates to explain this association. Low-cost foods are typically highly processed, composed of refined grains with added sugars and added fats, inexpensive, and palatable. Such foods combine low cost with high energy density and high reward value, are readily available in underserved areas (255), and tend to be preferentially selected by lower income groups (256, 257). Excess consumption of such foods is linked to rising obesity rates (258, 259), and it has been suggested that (for some individuals) consumption of such foods mitigates the stress of daily life (260–263), thereby adding to their high inherent reward value.

Studies that link diverse aspects of the built environment with diet quality metrics, reported physical activity, and weight and health outcomes have identified proximity to supermarkets, grocery stores, and other services, as well as access to parks and other opportunities for physical activity as independent predictors of obesity risk (249, 264–266). These and other studies (266–268) collectively identified an association between lower obesity rates and locations that have pedestrian safety; low crime; attractive streets; well-maintained parks; and homes within close physical proximity to supermarkets, parks, sidewalk cafes, and landmark buildings. Conversely, locations with physical disorder; poor sidewalk quality; close proximity to bars, liquor stores, fast food, and convenience stores; and the presence of garbage, litter, and graffiti were associated with higher BMI in some (269–271) but not other studies (272–274).

Residential property values provide insight into variations in the wealth of an individual or area; they also offer a useful alternative metric with which to assess the relationship between the built environment and obesity risk (275, 276). A Seattle-based study that examined the associations among perceived measures of the environment, residential property values, and BMIs (274) found that for each $100,000 increase in property value, obesity prevalence was 2.3% lower (254). Factors related to poverty or wealth may therefore account for at least some of the link between the built environment and obesity risk.

Access to healthy foods is one such measure. The concept of a "food desert," defined as a low-income area in which the nearest supermarket is at least 1 mile away (264), has become a focus of public health policies aimed at improving both diet and health (266,

274, 278). Studies suggest that BMI tends to be lower in areas where the consumption of vegetables and fruits is higher (279–281). Researchers tend to gauge a specific population's access to healthy food and food choices largely in terms of whether their neighborhood has a high density of (or long distance to) healthy food sources (282–285). Yet the risk of obesity is not reliably associated with distances between home and multiple food sources (281). Rather, it is the type of supermarket by price that is significantly associated with obesity rates, even after adjusting for the distance to the store and other sociodemographic and lifestyle variables.

Where obesity risk is concerned, therefore, access to healthier foods might be associated more with economics than with distance from home. This possibility highlights the need to focus beyond neighborhood geographic boundaries. One way to do this is to use GPS tracking methods that capture actual food shopping behaviors (286). Whether improved access of low-income populations to healthy foods will reduce obesity prevalence is an important unanswered question that the food desert formulation does not completely address.

Studies in the United States (287), United Kingdom (288), France (289, 290), Finland (291), Belgium (292), Ireland (293), and Australia (294) have reported that diet quality is directly linked to SES. Studies on food pattern modeling suggest that imposing a cost constraint leads to food choices that are energy-dense but nutrient-poor, similar in composition to diets consumed by lower income groups (295, 296). Recent economic analyses of empirical data from the United Kingdom provide a relevant example (297). In the wake of the economic recession of 2008, more British consumers turned to foods with lower cost per calorie (297), and obesity rates in the United Kingdom increased dramatically in recent years; today they are the highest in Europe (283). We need additional studies to investigate the extent to which economically driven dietary changes contributed to the observed increase of obesity prevalence.

Overall, these observations support the testable hypothesis that obesity risk increases among lower income groups when their food budgets are insufficient to ensure access to a healthy diet. This hypothesis points to the larger question of how such an effect ultimately causes not only weight gain but also the biological defense of elevated fat mass—the two processes that define the obese state. To reiterate a key point, factors that predispose to positive energy balance alone are insufficient to explain how obesity persists, because individuals who are obese defend their body-fat stores as effectively as do lean individuals (283), and switching to a "healthy" diet and lifestyle is insufficient to restore elevated body weight to normal in the vast majority of individuals (298). In addition to predisposing to weight gain, therefore, dietary, behavioral, and other factors linking SES status to obesity risk must also affect the energy homeostasis system in ways that raise the defended level of body adiposity. Studies that clarify how this occurs are a key priority for the field.

Diet composition, lifestyle, and obesity risk

Although an increase of average energy intake relative to energy expenditure during the past 3 to 4 decades can be inferred from the mean increase of adult body weight (>10 kg) in the United States (299), the relative contributions of increased energy intake and reduced physical activity to this increase cannot be known with certainty, nor can the extent to which energy balance is impacted by other variables [*e.g.*, sleep deprivation, decreased variation in environmental temperature (owing to heating and air conditioning), drugs causing weight gain, decreased smoking, and possible developmental exposures discussed earlier] (300). Although data from Swinburn *et al.* (301–303) suggest that increased energy intake is sufficient to account for recent population increases of body weight without invoking large decreases of physical activity, epidemiological evidence points to a concomitant increase of sedentary behaviors. For example, Church *et al.* (304) reported that energy expenditure related to occupation has drastically decreased over time, and that the associated reduction of energy expenditure likely contributes to the increase of mean body weight in the United States.

Impact of diet composition on obesity risk

The extent to which changes in diet composition drive the obesity epidemic has been a matter of considerable controversy for decades. To what extent does consumption of highly processed foods (especially snack foods) with higher levels of sugars and fats (and relatively low fiber) play a role? What about excess consumption of sugar-sweetened beverages, including soda, juice-based drinks, and sports drinks? These are questions of great public interest, particularly where diets high in fat vs carbohydrate content are concerned (305, 306).

Diets of different macronutrient composition can theoretically affect energy balance by altering overall caloric intake, energy expenditure, or both. However, available data argue against major effects on accumulation of body-fat mass, so long as energy intake is held constant (discussed further below). For this reason, the focus of the debate has shifted toward the effects of diet composition on caloric intake.

Substantial debate surrounds the question of whether the effects of dietary lipids to increase both palatability and caloric density contribute to their overconsumption (307, 308) or whether increased dietary carbohydrate content (and the associated insulin response, in particular) plays a uniquely important role in obesity pathogenesis (27, 309–311). As noted earlier, researchers have suggested that dietary carbohydrates—and refined sugars in particular—increase insulin secretion. This suppresses lipolysis and the associated release of fatty acids from the adipose tissue while also preferentially directing dietary fat toward storage. Some researchers propose that the

ensuing depletion of circulating fatty acids triggers a state of "cellular starvation" for metabolically active tissues, such as heart, muscle, and liver. Such changes might then induce both an adaptive decrease of energy expenditure (312) and an increase of food intake (27, 310, 313) that together conspire to cause obesity. Extending this logic, replacing dietary carbohydrate with fat should reduce insulin secretion while increasing fat mobilization and the oxidation of circulating free fatty acids, effects that together protect against obesity.

A number of observations challenge this premise. For one, despite the known ability of insulin to inhibit adipocyte lipolysis, and despite the fact that in uncontrolled diabetes severe insulin deficiency causes unrestrained lipolysis, there is little direct evidence that insulin's antilipolytic action is an independent determinant of fat mass. Furthermore, the hyperinsulinemia of obesity is typically associated with normal or elevated circulating glucose and fatty acid levels (314), a combination inconsistent with a state of insulin-mediated cellular starvation.

The foregoing discussion raises the perennial question: Is a calorie a calorie? In other words, can consumption of different types of foods predispose to weight gain independently of the number of calories consumed? To address this question, one study placed 17 volunteers who were obese or overweight on an isocaloric ketogenic diet (5% carbohydrate) for 4 weeks. This study revealed a marginal (~100 kcal/d) but statistically significant effect of the ketogenic diet to increase 24-hour energy expenditure measured in a respiratory chamber (28), but the effect waned over time and was not associated with significant loss of fat mass. This finding is consistent with other studies showing that carbohydrate restriction does not increase energy expenditure unless accompanied by an increase in protein content (as is the case in most low carbohydrate diets, but not the study described above) (315–317).

When calorie intake is held constant, therefore, body-fat accumulation does not appear to be affected by even very pronounced changes in the amount of fat vs carbohydrate in the diet. With regard to obesity risk, the clear implication is that the impact of a change of diet composition is primarily due to the number of calories consumed, with changes of energy expenditure, fat oxidation, or other aspects of nutrient handling being less important. Given that diets high in simple sugars and processed carbohydrates tend to be calorie-dense, low in satiety-promoting fiber and other nutrients, affordable, widely available, and often heavily marketed, it is perhaps not surprising that such diets can favor an increase of overall energy intake. In comparison, mechanisms related to increased insulin secretion, nutrient partitioning, cellular starvation, or other internal processes do not appear to explain the putative benefits of low-carbohydrate or low-glycemic index diets. Furthermore, a recent review of weight-loss diets (318) reported that although low-carbohydrate, higher fat diets led to slightly greater weight loss than did low-fat diets (~1 kg), the overall difference was trivial and does not justify recommending one diet over the other for weight-loss purposes. Although low-carbohydrate diets have been suggested to be helpful—by virtue of increased energy expenditure—for maintaining reduced body weight (315), differences in protein content of the comparison diets confound this conclusion.

Roles of sedentary behavior, exercise, and nonexercise activity thermogenesis

As mentioned earlier, the increasing global prevalence of obesity may involve sedentary behavior in addition to changes of food availability and/or diet composition. Analyzing the contribution of physical activity to total daily energy expenditure and obesity risk is a complex challenge. Although originally described as a single component of total daily energy expenditure (in addition to basal metabolic rate and diet-induced thermogenesis), overall physical activity can be subdivided into three distinct components: sedentary behaviors, nonexercise activity thermogenesis (NEAT), and planned/structured activity (exercise). Researchers estimate that during the past 50 years reductions in occupational physical activity have decreased total daily energy expenditure by >100 calories per day (304).

Physical activity is now widely accepted to be the most variable component of daily energy expenditure in people. Surprisingly, however, increased physical activity is largely ineffective as a stand-alone weight loss intervention, even though it should promote negative energy balance as effectively as does dietary energy restriction (319). The explanation for this paradox is presumably that among those individuals susceptible to obesity, the energy homeostasis system compensates for increased energy expenditure (by increasing energy intake and thus resisting weigh loss) better than it compensates for increased energy intake (by increasing energy expenditure to protect against weight gain). Nevertheless, adherents to vigorous physical activity programs are more likely to keep lost weight off than are those who remain relatively inactive. For example, according to the National Weight Control Registry, individuals who lose a substantial amount of weight and keep it off for an extended period of time, on average, are those who engage in at least 60 minutes per day of physical activity (320). This effect of exercise may involve a partial reversal of the effects of weight loss to increase muscle work efficiency (321). The key point is that although increased physical activity has not proven effective as a stand-alone treatment of obesity, it can help to sustain weight loss achieved by other means.

In addition to structured activity, Levine *et al.* (322) reported that energy expended passively in activities of daily living is both a determinant of total daily energy expenditure and an obesity risk factor. NEAT activities are those that occur during normal daily life, rather than in structured bouts of exercise (322) (*e.g.*, sitting; standing; fidgeting; walking; computer work; house-related chores; activities associated with personal

hygiene, such as bathing; and occupation-related activities). Evidence that reduced NEAT contributes independently to obesity pathogenesis stems from the observations that NEAT tends to be lower in individuals who are obese vs lean, and it does not appear to change in response to either weight gain (in normal weight subjects) or weight loss (in subjects who are obese) (322). With regard to the magnitude of this effect, a study of 177 individuals conducted in the late 1980s using a room calorimeter (323) found that energy expenditure attributable to spontaneous physical activity averaged 348 kcal/d but varied from 138 to 685 kcal/d between individuals. We need additional research to establish the extent to which variations in NEAT play a causative role in obesity pathogenesis.

Other factors

Smoking cessation

Another potentially causative factor in the steady increase of obesity prevalence in the United States and other Westernized societies is a substantial concomitant reduction in rates of cigarette smoking. Smoking cessation is reliably associated with weight gain (324), presumably owing to withdrawal of the pharmacological effect of nicotine to suppress food intake and weight gain. Nicotinic acetylcholine receptors are found on hypothalamic POMC neurons, and activation of these receptors can reduce food intake and body weight in animal models (325). Although reduced tobacco use can therefore be expected to increase the average body weight of a population, obesity nevertheless remains a problem among both current smokers and those who have never smoked.

Infectious factors

The emergence of obesity as a global pandemic has spurred interest in the hypothesis that one or more infectious agents play a causal role. Consistent with this view, individuals who are obese have a reduced immune response to some vaccines, raising the possibility that susceptibility to infections could play a role in the development of obesity. For example, infection with the AD-36 virus is reported to cause adipocyte proliferation and increased body weight in a variety of preclinical models, and individuals who are obese have significantly higher antibody titers to this virus than do lean individuals (326). However, without better evidence of a causal relationship between such infectious agents and human obesity, this mechanism seems unlikely to be a major factor underlying the current obesity epidemic. Should such evidence one day emerge, it would profoundly impact current approaches to obesity treatment and prevention.

Mechanisms for biological defense of elevated body-fat mass

Although the many intrinsic (*e.g.*, genetic) and extrinsic (*e.g.*, diet composition, lifestyle, or SES) variables discussed herein can favor positive energy balance and predispose to weight gain, a fundamental unanswered question is how elevated body-fat mass comes to be biologically defended in individuals who are obese. Under certain circumstances (*e.g.*, mutation of genes encoding leptin or POMC) we can predict that the biologically defended level of body fat will increase due to the direct, deleterious effects on the energy homeostasis system. In the vast majority of individuals who are obese, however, researchers have yet to identify a clearly definable energy homeostasis defect (genetic or otherwise) to explain this phenomenon. Part of the experimental problem is that subtle differences in energy intake and/or expenditure can have large effects on adiposity over time, and once an individual is in weight equilibrium, any etiological differences are no longer present.

A very modest but persistent energy balance mismatch (~1% to 3% more calories consumed than expended per year) can explain the slow but continuous accumulation of additional body fat over many years that is characteristic of most humans who are obese. Although an acute increase of body-fat mass is often reversible, incremental, sustained increases of body fat typically end up becoming part of the total body-fat mass that is biologically defended. It is for this reason that the weight loss induced by a change of diet or lifestyle (*e.g.*, changes that might be expected to remedy an acquired defect in the energy homeostasis system arising from a maladaptive diet, sedentary behavior) is often ultimately regained, even in the face of adherence to a more healthy diet and lifestyle. These observations imply that although the mechanism underlying the gradual increase in the defended level of body fat may have been triggered by one or more of the many environmental exposures discussed earlier, simple withdrawal of the offending exposure is unlikely to reverse the increased body fat once it becomes established. Instead, the energy homeostasis system has been upwardly reset, so that the higher level of body fat is relatively resistant to lifestyle interventions, similar to a genetically determined increase of adiposity (although not necessarily by the same mechanisms).

How might such a change in the energy homeostasis system be acquired? Although we still wait for definitive answers, recent work offers potential insights. In many tissues (including liver, skeletal muscle, adipose tissue, and the vasculature) obesity is associated with activation of inflammatory processes marked by the invasion of macrophages or related immune cells and an associated increase in the expression of proinflammatory cytokines, such as tumor necrosis factor-α or interleukin-1 (327). Because the onset of this inflammation either coincides with obesity onset or occurs after obesity is established, it is likely a consequence rather than a cause of obesity (327). However, the hypothalamus is an exception. In this region of the brain inflammation and tissue injury occur in discrete areas involved in energy homeostasis, and this effect is evident before obesity develops. When rats or mice are placed on an HFD,

inflammatory markers become detectable in the hypothalamic ARC within 24 to 48 hours, well before body-fat mass has increased (328). Moreover, this inflammatory response is associated with expansion and activation of hypothalamic glial cells, a process referred to as "reactive gliosis" (the prototypical brain response to neuron injury). Specifically, switching either mice or rats from standard chow to a HFD (which predisposes to diet-induced obesity) induces both microgliosis and astrogliosis (activation of microglia and astrocytes, respectively) in the ARC within 1 week (328, 329).

Although it is tempting to draw a causal link between the evidence of injury to a key brain area for energy homeostasis and defense of elevated body-fat mass, we emphasize that neither the causes nor the consequences of this local hypothalamic reaction to HFD feeding are known. Thus, the idea that the defense of elevated fat mass results from this hypothalamic gliosis (by impairing the capacity of key neurons to respond to input from leptin and/or other pertinent humoral/neural signals) is a hypothesis that needs further testing. A working model posits that in susceptible animals or humans, an increase in the consumption of saturated fat (329) and/or other nutrients induces injury of hypothalamic neurons involved in energy homeostasis, which in turn triggers reactive gliosis. Alternatively, the diet switch may directly activate local microglia (a macrophage-like cell found only in the central nervous system), a response that sets off a vicious cycle by causing neuron injury and triggering more gliosis. In either case, it is not difficult to envision how this type of local reaction might dampen the capacity of ARC neurons to respond to humoral (leptin) or neural inputs relevant to body weight control and thereby favor the defense of elevated body-fat mass. It is noteworthy that studies have reported radiological evidence of gliosis in the mediobasal hypothalamus in humans who are obese (328, 330), as well as in rodent models. What distinguishes this type of mechanism from those discussed earlier is its potential to account for the defense of elevated body weight in acquired (environmental) forms of obesity. The extent to which it does so is a key priority for future work.

Concluding Remarks and Future Directions

In closing, we attempt to distill from foregoing sections a set of key areas for possible further investigation.

The two distinct components of obesity pathogenesis

To be viable, theories of obesity pathogenesis must account not only for how excess body fat is acquired, but also for how excess body fat comes to be biologically defended. To date, the preponderance of research has focused on the former. However, we must consider the possibility that some (perhaps even most) mechanisms underlying weight gain are distinct from those responsible for the biological defense of excess fat mass. A key question, therefore, is how the energy homeostasis system comes to defend an elevated level of fat mass (analogous to the defense of elevated blood pressure in patients with hypertension). Answering this question requires an improved understanding of the neuromolecular elements that underlie a "defended" level of body fat. What are the molecular/neuroanatomic predicates that help establish and defend a "set point" for adiposity? How do these elements regulate feeding behavior and/or energy expenditure, so as to achieve long-term energy balance? By what mechanisms is an apparently higher set point established and defended in individuals who are obese?

Given that recovery of lost weight (the normal, physiological response to weight loss irrespective of one's starting weight) is the largest single obstacle to effective long-term weight loss, we cannot overstate the importance of a coherent understanding of obesity-associated alterations of the energy homeostasis system.

Developmental determinants of the biologically defended level of body-fat mass

By what means do intrauterine, perinatal, and later developmental processes influence the defended level of body fat or set point? How do these factors interact with underlying genetic determinants? Is overnutrition during development associated with premature maturation of feeding circuits? Can insight into key developmental influences be leveraged into strategies to reset the defended level at a lower value? Can these insights enable us to prevent the homeostatic system from being reset at a higher level in the first place? Do these developmental exposures act directly on energy balance neurocircuitry, or do such effects occur indirectly as a result of nonspecific changes in rates of placental or fetal growth that impact adult body weight and composition? Answers to these questions will potentially help us develop maternal/prenatal interventions that could protect against obesity in adulthood.

Interactions between genetics, epigenetics, developmental influences, and the environment

Although many studies (*e.g.*, those based on identical twins reared apart) identify a major role for heritable factors as determinants of obesity susceptibility, GWAS data indicate that only a small fraction (~10%) of obesity risk is attributable to identifiable allelic variants. One potential explanation for this discrepancy is that nongenetic factors that contribute to heritability, such as epigenetic modification or developmental influences, make a major contribution to obesity risk. Another possibility is that interactions among risk alleles themselves and/or between risk alleles, epigenetic factors, and developmental factors play a role. Beyond these considerations, each of these

potential contributors to obesity risk can interact with environmental factors as well. In other words, many heritable factors may increase obesity risk, not by causing obesity so much as by conferring susceptibility to obesogenic environmental factors. It seems plausible, for example, that certain obesity risk alleles expressed in the brain, perhaps through an interaction with neurodevelopmental consequences of gestational events, enable energy homeostasis neurocircuits to become reset around a higher level of body fat stores. It is also possible that the likelihood of such an outcome is maximized by consuming a diet that is highly palatable, energy dense, and in abundant supply. Establishing suitable experimental models with which to test such concepts is a necessity.

Future directions for EDC research

Although available evidence suggests that EDCs can impact the function of genes important for the control of energy balance and adipocyte function, human data and results from *in vivo* animal studies have yet to clearly demonstrate an increased risk of obesity conferred by developmental EDC exposure. Among the confounding factors that may underlie this uncertainty are differential developmental impacts of EDC exposure on metabolically relevant organs (*e.g.*, liver and adipose tissue) (331, 332), variation stemming from sex- and dosage-specific effects, and the potential for combinations of EDCs to cause synergistic effects (181, 184, 193, 194). These concerns highlight the need to focus animal research on those exposures most closely linked to untoward impacts on child health. Meta-analyses of prospective epidemiological data may ultimately help to identify those combinations and doses of EDC exposures that are most often associated with increased adiposity and that are observed consistently across species. Studies that define conditions in mice that recapitulate the molecular and/or epigenetic signatures of EDC exposure in humans will also be important (331, 332). Given difficulties inherent in obtaining human tissue, the identification of biomarkers for these effects (*e.g.*, changes of liver function) may also help to accelerate progress in this field. Lastly, the question of whether developmental EDC exposure increases obesity risk through nonspecific effects on fetal growth (193), rather than or in addition to direct effects on energy homeostasis system components, must be addressed.

Lessons learned from the weight-reduced state

The weight-reduced state is a distinct metabolic/behavioral condition created when body weight is reduced below its biologically defended level. Studies during the past 30 years (9, 321, 333–337) have shown that maintenance of a reduced body weight (*e.g.*, 10% or more) is associated with reductions in energy expenditure (in part conveyed by increased contractile efficiency of skeletal muscle) due to reduced sympathetic autonomic activity and circulating thyroid hormones. Reduced body weight increases hunger as well, creating a "perfect metabolic storm" for weight regain (338). It also reduces circulating leptin concentrations in proportion to lost body fat, and (consistent with the leptin threshold formulation described earlier) providing exogenous leptin in doses just sufficient to restore circulating leptin to preweight loss concentrations relieves some of the autonomic, endocrine, energy expenditure, and behavioral phenotypes associated with the weight-reduced state (321, 335). Whether such "physiological leptin replacement" strategies can protect against recovery of lost weight is an important unanswered question.

Rather than viewing recovery of lost weight as a therapeutic failure or as evidence of noncompliance with a prescribed treatment regimen, patients and practitioners alike should view this phenomenon as an expected physiological response to weight loss. This perspective emphasizes the importance of identifying strategies to subvert these responses. It is likely that the pharmacology involved in maintaining the weight-reduced state is different—qualitatively and quantitatively—from that relevant to the induction of weight loss. The Food and Drug Administration should allow for such differences in the licensing of pharmacologic agents for the treatment of obesity.

The gut–brain axis

There are a number of key questions pertaining to the gut microbiome. Does it influence the defended level of body-fat mass and, if so, to what extent? How do microbial influences interact with the energy homeostasis system? To what extent do host genetic or other variables influence such effects? Is the microbiome a potential target for obesity treatment? How do bariatric surgical procedures, such as Roux-en-Y gastric bypass or vertical sleeve gastrectomy, reduce the biologically defended level of body-fat stores? Which specific signals emanating from the GI tract account for this phenomenon?

Identifying the relevant signals and delineating how they influence energy homeostasis neurocircuitry will ultimately inform potential drug-therapy targets.

Dietary influences

Growing evidence suggests that (for practical purposes) the answer to the question, "Is a calorie a calorie?" is "yes." Calories derived from different dietary constituents (fats, carbohydrates, and proteins) do not differ significantly in their inherent capacity to promote weight gain by affecting energy expenditure or nutrient partitioning, so long as total calorie intake is held constant (339). From this we infer that the effects of diet composition *per se* on metabolic variables suggested to contribute to obesity pathogenesis (*e.g.*, those related to plasma levels of glucose, insulin, or free fatty acids; inherent differences in the propensity of adipocytes to store fat; or the gut microbiome) do not play a clinically significant causal role unless they promote increased calorie intake (340). The therapeutic potential of interventions primarily targeting these metabolic processes *per se*, therefore, seems limited.

Stratification of obesity outcomes

Given that not all individuals who are obese are subject to the same level of risk of comorbidities, we need improved strategies for identifying biomarkers predictive of these comorbidities (*e.g.*, diabetes, hypertension, dyslipidemia, and cardiovascular disease). Similarly, strategies for identifying both predictors of future obesity comorbidity risk (to enable effective preventive intervention) and responsiveness to a specific therapeutic intervention (to improve outcomes by identifying what intervention is best suited for each individual) are also a high priority.

Unraveling mechanisms linking the environment to defense of elevated body weight

A seemingly unlimited number of environmental variables appear to predispose to weight gain. Poverty is a case in point. How does its influence on food choices, behavior, and activity translate to increased obesity risk? How can we best account for the impact on obesity risk of differences in the racial and ethnic mix between low and higher SES communities? Do developmental factors also contribute?

Disarticulating differences in genetic background from the impact of diet, lifestyle, and other environmental variables is a daunting challenge. That the impact of low SES on obesity risk is greater among women than men (339) points to poorly understood interactions between environment and biology that influence obesity risk. Studies that delineate how interactions among these factors impact the energy homeostasis system are critical.

Identifying and mitigating environmental risk factors

Taking poverty again as an example, does an identifiable set of motivations, attitudes, and beliefs contribute to obesity susceptibility? Which specific elements related to SES predispose not only to weight gain but to the biological defense of elevated body-fat stores, and how might they be mitigated? Can such mitigation efforts reduce obesity risk?

Translating basic science into more effective pharmacotherapy

Can anatomic and functional imaging of the human brain be used, in combination with suitable behavioral measures, to translate cognitive, regulatory, and hedonic aspects of human feeding behavior into effective new pharmacologic approaches to the treatment of obesity? An improved understanding of those aspects of ingestive behavior that are not driven directly by homeostatic mechanisms controlling body weight is critical to strategies for obesity prevention. Insight gained from animal models of these "hedonic" processes may eventually identify relevant pathways and molecules. However, we will need better behavioral and imaging tools to fully understand these phenotypes in humans.

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Acknowledgments

We acknowledge science writer Eric Vohr for his contribution to this scientific statement, and Drs. William Heisel and Ashkan Afshin of the Institute for Health Metrics and Evaluation at the University of Washington for their helpful comments.

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This work was supported by National Institutes of Health Grants DK083042, DK090320, and DK101997 and by the National Institute of Diabetic and Digestive and Kidney Disease–funded Nutrition Obesity Research Center at the University of Washington (to M.W.S.), R01 DK089038 (to L.M.Z.), DK52431 (to R.L.L.), DK076608 (to A.D.), DK072476 (to L.M.R. and E.R.), and the Russell Berrie Foundation (to R.L.L.).

Disclosure Summary: M.W.S. receives research funding from and serves as a consultant to Novo Nordisk. R.J.S. receives research support from Ethicon/Johnson & Johnson, Novo Nordisk, Janssen/Johnson & Johnson, MedImmune, Sanofi, and Boehringer-Ingelheim, and serves as a consultant/advisor to Ethicon/Johnson & Johnson, Novo Nordisk, Orexigen, Daiichi Sankyo, Janssen/Johnson & Johnson, Novartis, Paul Hastings Law Firm, Zafgen, Takeda, and Boehringer-Ingelheim. A.D. has received grants, contracts, honoraria, and consulting fees from numerous food and beverage companies and other commercial and nonprofit entities with interests in diet quality and health. E.R. serves on the Scientific Advisory Board to the Nutrilite Health Institute with Amway, has a consultant contract with Janssen, serves on the Scientific Advisory Board for the Institute of Cardiometabolism and Nutrition in Paris, France, gives lectures at the Open Academy in Venice, and is an advisor for the Center for Medical Weight Loss. He has received research grants or unrestricted gifts from Amway, Nestle, the Nutrition Science Initiative, and Ethicon Surgery. L.M.R. serves on the Scientific and Medical Board Advisor to AdvoCare International, LP, and receives royalties for SmartLoss® and SmartMoms®, which are intensive weight management interventions delivered via mHealth technology. The remaining authors have nothing to disclose.

Abbreviations

AgRP, agouti-related protein; ARC, arcuate nucleus; BAT, brown adipose tissue; BMI, body mass index; BPA, bisphenol A; $CGRP^{PBN}$, calcium gene-related peptide expressing neurons in the parabrachial nucleus; EDC, endocrine-disrupting chemical; GABA, γ-aminobutyric acid; GI, gastrointestinal; GWAS, genome-wide association study; HFD, high-fat diet; iBAT, interscapular brown adipose tissue; LPL, lipoprotein lipase; NEAT, nonexercise activity thermogenesis; NPY, neuropeptide Y; PFC, perfluorinated chemical; POMC, proopiomelanocortin; SES, socioeconomic status.