Beyond Energy Balance: There Is More to Obesity than Kilocalories

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ABSTRACT
Using an epidemiologic model of the interactions between environmental agents and human hosts to explain obesity, we explored food, medications, physical inactivity, toxins, and viruses as environmental agents that interact with a genetically programmed host to disturb energy balance and cause obesity. Large portion sizes, high fat intakes, easy access to calorically sweetened beverages, and lack of any need to be physically active all play a role in the toxic environment that leads to obesity. The genetic and physiologic responses of a host determine whether or not this toxic environment will produce obesity. Reversing the current trends of obesity requires a new look at the limits of the energy balance concept, and a better understanding of how environmental factors acutely and chronically change the responses of susceptible hosts.


Obesity is a chronic, relapsing, stigmatized, neuro-chemical disease that is increasing in prevalence (1,2). During the early part of the 20th century the prevalence of obesity rose slowly, but around 1980 it began to rise more rapidly. Children are affected by obesity, with the prevalence rising from 5% in 1960 to 15% in 2000 (2). Associated with this rise in obesity rates was an increase in the prevalence of type 2 diabetes mellitus in children and adolescents (3). This presages a dire future for these children as complications of blindness, heart disease, renal failure, and amputation disable them during the next 20 years or so.

Obesity increases health risk and the cost of health care (4). Diabetes mellitus, gall bladder disease, heart disease, hypertension, osteoarthritis, and several types of cancer are all increased in persons with overweight. These risks can be reversed by modest weight loss. To tackle the hazards of obesity for children, adolescents, and adults, we need to adopt effective strategies for prevention and, where prevention fails, for treatment of obesity. Many children and adults with overweight are traumatized by the stigma of obesity. Children may be teased at school and labeled “fatty.” Adults experience prejudice in social and economic situations. Measures of quality of life show that persons with obesity score lower on many scales and that weight loss improves their quality of life.

BEYOND ENERGY BALANCE
There is no doubt that obesity results from energy imbalance, and that we can predict the magnitude of weight change over time if we know the net energy balance. However, it is what the energy balance concept does not tell us that is most important in dealing with obesity. The first law of thermodynamics, which describes the concept of energy balance, does not tell us anything about the regulation of food intake or the way in which genes are involved in this process. It does not help us to understand why men and women distribute fat in different places on their bodies, or to understand how fat distribution changes with age. The first law also doesn’t help us understand why some drugs produce weight gain and others weight loss, or why weight loss stops after a period of treatment with diet or medication (5). Understanding these mechanisms will allow us to tackle the epidemic of obesity.

Another problem with the concept of energy balance is that we are never in energy balance. To study energy balance, we housed healthy men in small rooms (respiration calorimeters) where we manipulated food intake and exercise to get as close as possible to zero energy balance; ie, when energy intake equals energy expenditure. In fact, we rarely got closer than 50 kcal/day, or about 2.5% out of an intake of 2,000 kcal/day. The values for energy imbalance in these healthy men ranged from 50 to 150 kcal/day. Had these differences been maintained for 1 year, these men would be expected to gain about 2.5 kg (5.5 lb) at the smaller error and 7.5 kg (16.5 lb) at the larger error. To keep from gaining weight we must correct energy intake or energy expenditure every few days to counterbalance the error that occurred on previous days. These corrective responses around a weight of relative stability make it look like there is weight regulation. For some persons, the oscillations around this balance point can keep weight stable for many years. For others, there is a slow upward drift in this regulatory point and weight gain is gained gradually. Persons fortunate enough to have robust corrective responses can maintain a stable weight over many years. If their weight is not stable, two other
strategies are available. One is conscious control, exhibited in some persons by a pattern of restrained eating. The second and perhaps best way to maintain weight over a long period is not counting kilocalories, but weighing oneself regularly at the same time of day on an accurate scale, and then decreasing food intake or increasing activity if weight has been gained. This can allow one to correct weight gain before it gets out of hand.

The consequences of energy imbalance are graphically illustrated in the movie by Morgan Spurlock, *Supersize Me* (2004, Hart Sharp Video, Roadside Attractions, and Samuel Goldwyn Films), in which the documentarian gained 25 lb in 1 month by eating all of his meals at McDonald’s restaurants, and supersizing the portions if the clerk asked. Because we are never in energy balance, we need to view energy balance as an ideal—not a realistic goal to be obtained by counting kilocalories.

From the perspective of energy balance, the solution to obesity should be simple: Eat less and exercise more. The truth of this advice was shown by Kinsell and colleagues (6) for overweight persons in a metabolic ward who were provided with all of their food. During the course of several months, patients ate diets providing 1,200 kcal/day. After an initial rapid weight loss due to rebalancing body fluids, subsequent weight loss was linear and was not affected by wide variations in macronutrient content of the diet. More recent studies using foods that were tagged with a nonradioactive isotope (carbon-13) showed that the better the adherence to a diet, the greater the weight loss (7). Thus, it is adherence to diets, not diets themselves, that makes the difference (8).

Another limitation to the concept of energy balance as the cause of obesity is the implication that if one is getting fatter, it is one’s own fault. One need only to control his or her energy intake and energy expenditure to control the problem. This implies that we should blame our children for their obesity. This seems grossly unfair. If obesity were easily controlled by moderating energy intake, the US military would not discharge up to 5,000 men and women yearly for failing to meet its weight standards. If loss of livelihood is not sufficient motivation to lose weight, then the problem must be more complex.

The cure of obesity in leptin-deficient human beings treated with leptin shows a genetic basis for one type of obesity, and that obesity is more than simply lack of willpower (9). Although simple in theory, applying the ideas of energy balance and counting kilocalories to body weight control has proven unsuccessful. More than 95% of persons using diet, behavior, and lifestyle approaches to lose weight regained it in less than 5 years (10).

ENVIRONMENTAL AGENTS

The current epidemic can be viewed from the perspective of an epidemiologic model, shown in Figure 1. Food, drugs, viruses, toxins, and low physical activity are the environmental agents that facilitate the development of obesity. One or more of these factors acting on a susceptible host can produce obesity. Using this model, we can approach the problem by manipulating either the environment or the host.

Figure 1. Epidemiologic model of obesity. In this model, the agent that produces obesity is food or food-related products. If food is in limited supply, obesity does not develop. The food that is ingested interacts with the host. In a susceptible host, the toxic effects of food produce the disease of obesity.

Food

As the spokesperson for the Grocery Manufacturers of America said in the movie *Supersize Me*, “The food industry is part of the problem.” Several components of our food supply may be important in determining whether or not obesity develops. The first of these is the portion size of packages and servings. There is convincing evidence that when larger portion sizes are provided, more food is eaten (11). Portion sizes have dramatically increased in the past 40 years (12) and now need reduction. Calorically sweetened beverages that contain 10% high-fructose corn syrup (HFCS), available in containers of 12, 20, or 32 oz, provide 150, 250, or 400 kcal if it is all consumed. Many foods list the kilocalories per serving, but the package often contains more than one serving.

Patterns of food consumption have changed during the past 30 years (13). The most striking change from 1970 to 2000 was in the rising consumption of HFCS (14). HFCS is now used as the caloric sweetener in almost all soft drinks as well as in reconstituted juice drinks and many solid foods. The rise in HFCS consumption occurred during the same time interval as the rapid rise in the prevalence of obesity (2,14). On one hand, this relationship may be strictly coincidental. But, on the other hand, it may not (Figure 2). Fructose is sweeter than glucose, or sucrose, a molecule that is a combination of fructose and glucose. In addition, HFCS is a solution of both fructose and glucose as separate molecules, and thus it differs in osmotic properties from a solution with the same concentration of sucrose.

The intake of calorically sweetened beverages can be related to the epidemic of obesity (14-17). Ludwig and colleagues (15) reported that the intake of soft drinks was a predictor of initial body mass index (BMI) in children in the Planet Health Study. They also showed that higher soft drink consumption predicted an increase in BMI during nearly 2 years of follow-up, those with the highest soft drink consumption at baseline having the highest increase in BMI. A Danish study (16) showed that persons consuming calorically sweetened beverages over 10 weeks gained weight, whereas subjects drinking the
same amount of artificially sweetened beverages lost weight. In children, a study focusing on reducing intake of carbonated beverages and replacing them with water showed slower weight gain than those not advised to reduce the intake of carbonated beverages (18). These studies strongly suggest that energy-containing soft drinks could play a role in the epidemic of obesity. If so, then their consumption should be curtailed, particularly for very young children in whom neuronal changes may reflect the response of insulin to these beverages, and for school children for whom beverages are a ready source of energy with few other nutrients.

Dietary fat is another component that may be related to the epidemic of obesity (19). Foods combining fat and sugar may be a particular problem because they are often very palatable and usually inexpensive (20). The Leeds Fat Study (21) showed that persons who were high fat consumers had an increased prevalence of obesity. Providing palatable low-fat foods is important.

There are now several studies showing that when breastfeeding is the sole source of nutrition for more than 3 months, risk of obesity is significantly reduced at the time of entry into school and in adolescents when compared with infants who are not breastfed at all or for less than 3 months (22). This may be an example of infant imprinting. The composition of the breast milk may also be important. During the past 50 years, the proportion of n-6 fatty acids in human breast milk has increased, reflecting changes in dietary fat composition. The amount of n-3 fatty acids in breast milk has remained constant. A higher amount of n-6 fatty acids provides prostaglandin derivatives that stimulate fat cell proliferation in infants (23). This is a concept that needs additional evaluation. The rate of weight gain between ages 2 and 12 years also predicts future obesity—those children who gain the most weight have the highest risk of becoming obese (24). Monitoring weight change early can be predictive of future obesity.

Calcium intake is another dietary factor that may be related to the development of obesity in children and adults. The level of calcium intake in population studies is inversely correlated with the risk of being overweight. In other epidemiologic studies and in feeding trials, higher dietary calcium is associated with reduced BMI or reduced incidence of insulin resistance (25).

Low Levels of Physical Activity
Epidemiologic data show that low levels of physical activity and watching more television predict higher body weight (26). Recent studies suggest that persons in US cities where they had to walk more than persons in other cities tended to weigh less. Low levels of physical activity also increase the risk of early mortality. Using normal weight, physically active women as the comparison group, Hu and colleagues (27) found that the relative risk of mortality increased to 1.55 in inactive lean women, to 1.92 in active obese women, and to 2.42 in women who are obese but physically inactive. It is thus better to be thin than fat and to be physically active rather than inactive.

Drugs and Chemicals that Produce Weight Gain
Several drugs can cause weight gain, including a variety of hormones and psychoactive agents (28). The degree of weight gain is generally not sufficient to cause substantial obesity, except occasionally in patients treated with high-dose corticosteroids, some psychoactive drugs, or valproate. These drugs can also increase the risk of future type 2 diabetes mellitus. Cessation of smoking is another environmental agent that will affect body fat stores. Partially mediated by nicotine withdrawal, a weight gain of 1 to 2 kg is seen in the first few weeks and is often followed by an additional 2- to 3-kg weight gain over the next 4 to 6 months, resulting in an average weight gain of 4 to 5 kg or more (29). The concept that increasing energy expenditure through drugs that act like physical activity is being tested in several ways, but as yet no effective agents have been identified.

Viruses
The injection of several viruses into the central nervous system produces obesity in mice. Recent findings of antibodies to one of the adenoviruses (AM-36) in larger amounts in obese human beings raises the possibility that viruses are involved in some cases (30). The adeno-viral syndrome can be replicated in nonhuman primates and is characterized by modest obesity and a low circulating cholesterol concentration. Further studies are needed to establish that a syndrome of obesity associated with low concentrations of cholesterol clearly exists in human beings. If so, this would enhance the value of the epidemiologic model.

Toxins
In experimental animals, exposure in the neonatal period to monosodium glutamate, a common flavoring ingredient in food, will produce obesity. A similar effect of reduction in glucose can also produce obesity, suggesting that the brains of growing animals, and possibly those of human beings, may respond with damage to the metabolic sensors that regulate food needs. In human beings, body fat stores many toxic chemicals that are mobilized with

![Figure 2. The consumption of sweetened carbonated beverages and the relation of high-fructose corn syrup consumption (HFCS) to the epidemic of obesity.](image)
weight loss. The metabolic rate can be reduced by organochlorine molecules (31), and prolonged exposure to many chlorinated chemicals in our environment has conceivably affected metabolic pathways and energy metabolism. Food additives are another class of chemicals that are widely distributed and may be involved in the current epidemic of obesity.

**THE HOST**

**Genetic Factors**

Significant insight into the causes of obesity has come from the cloning of genes that produce obesity in animals. Extensive molecular and reverse genetic studies (mouse knockouts) have also helped establish critical pathways regulating body fat and food intake. Leptin, identified in 1994, is an important hormone produced in adipose tissue and secreted into the blood relative to the amount of body fat (32). Leptin-deficient persons are massively obese and when leptin is administered, food intake falls and body fat is mobilized until body weight is nearly normalized, indicating that important metabolic-genetic pathways exist that can control body fat. Similar deficiencies in food intake have been found with genetic changes in the amino acid sequence of a key regulator of food intake called the melanocortin-4 receptor (33). When this receptor is inactive, food intake is nearly as high as when leptin is deficient, but when partially preserved, the food intake is only modestly above control levels (34). These basic biological insights tell us that body fat has important regulation that is largely, if not completely, independent of will power.

**Intrauterine Imprinting**

Several intrauterine events may lead to obesity later in life, probably due to fetal imprinting as a result of early exposure that affects brain plasticity. The Dutch winter famine of 1945 showed that starvation of infants in utero could affect long-term postnatal weight status. Another example is the infants of mothers who smoked during pregnancy, who have an increased risk of becoming overweight during their first 3 decades of life when compared with infants of mothers who did not smoke during pregnancy (35). Similarly, infants of mothers with diabetes are at higher risk of developing obesity than infants born to mothers who did not have diabetes during pregnancy (36). Infants who are small for their gestational age are at higher risk of developing central adiposity and diabetes than normal-weight infants (24). Finally, experimental studies teach us that exposure to high levels of insulin during the period of brain plasticity can lead to obesity later in life.

**Physiologic Control**

To maintain a stable body weight over time, the body must correct daily errors in energy balance. A number of physiologic factors are known to disturb this correction. A high rate of carbohydrate oxidation, as measured by a high respiratory quotient predicts future weight gain (37). One explanation is that when carbohydrate oxidation is higher than carbohydrate intake, carbohydrate stores are depleted and we must eat to replace them. Persons with obesity who have lost weight are less effective in increasing fat oxidation in the presence of a high-fat meal than normal-weight persons, and this may be one reason why they are so susceptible to weight regain. Low metabolic rate may also predict future weight gain (38).

Physical activity gradually declines with age, accounting for some increase in body fat. Recent studies suggest moderate exercise is beneficial in reducing risk of cardiovascular disease (39) and type 2 diabetes, and in facilitating the oxidation of fat in the diet (40).

Fat cells in our body serve two major functions. They store and release fatty acids ingested from food or from liver or fat cells and they secrete many important hormones and chemicals. The discovery of leptin catapulted the fat cell into the arena of endocrine cells (41). In addition to leptin, the fat cell secretes a variety of other peptides (lipoprotein lipase, adipisin [complement D], complement C, adiponectin, tumor necrosis factor-alpha, interleukin-6, plasminogen activator inhibitor-1, angiotensinogen, bradykinin, and resistin). The fat cell also releases other metabolites such as lactate, fatty acids, glycerol, and prostaclin formed from arachidonic acid. Our understanding of fat cells as important endocrine cells continues to expand.

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Production of cortisol from inactive cortisone in fat cells by the enzyme 11-β-hydroxysteroid dehydrogenase type 1 may be important in determining the quantity of visceral adipose tissue (42). Changes in this enzyme may contribute to the risk for menopausal women of developing more visceral fat. High levels of this enzyme keep the quantity of cortisol in visceral fat high, providing a fertile environment for developing new fat cells.

Information about hunger and satiety comes from the gastrointestinal tract where several peptides signal the body to stop or start eating. Ghrelin (43) has received recent attention because, in contrast to other gastrointestinal hormones, it stimulates food intake. Levels of ghrelin are low in obesity, except in those with Prader-Willi syndrome, suggesting that it may play a role in the development of hyperphagia seen in these persons.

The brain is a receiver, transducer, and transmitter of information about hunger and satiety. Several neurotransmitter systems are involved in regulation of food intake (44). Receptors for serotonin modulate both the quantity of food eaten and macronutrient selection and their loss through genetic targeting produces obesity. Peptide neurotransmitters also play a very important role in the regulation of feeding. Sleep deprivation is one way to enhance the release of peptides that produce hunger (45). In young men allowed to sleep only 4 hours/night for 2 days, leptin decreased and ghrelin increased relative to the pattern seen with 10 hours of sleep on each of two
At least three preventive strategies are available to deal with the epidemic: education, regulation, and modification of the food supply.

We also argue that it is what the first law of thermodynamics does not tell us that is important. In this context, it is the unconscious host systems on which environmental factors operate to produce obesity. If the vending machines that now provide kickbacks to schools contained beverages with no added sugar or HFCS, available kilocalories would be reduced. We have argued that the exposure of young children to HFCS may produce detrimental imprinting of the brain, making obesity more likely and more difficult to control.

At least three preventive strategies are available to deal with the epidemic: education, regulation, and modification of the food supply. Education in school curricula about good nutrition and healthful weight would be beneficial in helping all children learn how to select appropriate foods and could be included in schools, with school breakfast and lunch programs designed to match these educational messages.

It is unwise to rely on educational strategies alone because they have not prevented the epidemic of obesity. Regulation is a second strategy. Regulating an improved food label is one good idea. Regulations on appropriate serving sizes might be part of the information provided by restaurants when requested.

Modification in some components of the food system is a third and most important strategy. Because the energy we eat comes from food, we need to modify this system to provide smaller portions and less energy density if we are to succeed in combating the epidemic of obesity.

**CONCLUSIONS**

Where do dietetics professionals fit into this picture? First, educated dietetic professionals need to be keenly aware of the complexity of the obesity problem. A dietetics professional obviously cannot alter a person’s genetic makeup, but he or she is able to address the environmental aspects that serve to exacerbate the situation. Simply handing out diet sheets is not enough and should be discouraged. Helping a patient with obesity requires attention to overall diet history, current eating habits, activity patterns, and behavioral obstacles that either cause problems or prevent change. While quick weight loss may be a patient’s immediate desire, the need for permanent lifestyle changes should be the primary objective. Tips for addressing this have been outlined previously by Bray and Champagne (47). Finally, dietetics professionals can be instruments of change by appealing to policymakers to modify environmental conditions, such as the school vending machines. We can think of no better professionals to craft this effective message to both lawmakers and school officials alike.

**FUTURE DIRECTIONS**

Our lives are constrained by the laws of nature—gravity, momentum, and thermodynamics. The strategies we employ to deal with the influence of these laws on our lives include education, regulation, and product design. Deaths resulting from the effects of the laws of momentum produced by automobile accidents provide a glimpse into the strategies we could use to minimize accidents just as the law of energy balance provides ideas about how we might minimize obesity. Although the laws of momentum or the laws of thermodynamics cannot be changed, their ability to produce automobile accidents and obesity can be mitigated. This can be done through better education about driving and about nutritional needs to prevent obesity. This can be complemented by regulations that, in the case of cars, include requiring seat belts, airbags, and other safety devices. In the case of obesity, it includes limiting access to large portion sizes and high-energy-density foods and having an environment in which physical activity is more difficult to avoid. Finally, product design can make cars safer, and modifying the types of foods that are available can provide strategies to combat the obesity epidemic by redesigning the food environment.

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**References**


