A War on Obesity, Not the Obese
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VIEWPOINT

A War on Obesity, Not the Obese

Jeffrey M. Friedman

In their efforts to lose weight, obese individuals may be fighting a powerful set of evolutionary forces honed in an environment drastically different from that of today.

Food consumes our interest. To the hungry, it is the focal point of every thought and action. To the hundreds of millions of obese and overweight individuals, it is the siren's song, a constant temptation that must be avoided lest one suffer health consequences and stigmatization. To the non-obese, it is a source of sustenance and often pleasure. To the food and diet industries, it is big business. And to those interested in public health, it is at the root of one of the most pressing public health problems in the developed and developing world.

Alarm about obesity is sounded almost weekly in response to reports that its incidence has increased significantly over the past decade, along with a concomitant rise in its dreaded health consequences: diabetes, heart disease, and hypertension (*1*). Why is it that so many of us are obese? What has changed in such a short period of time to make us obese? Who is at fault? The food industry? The obese? Parents for not insisting that their children eat less and exercise more? The medical and scientific community, for not having found a satisfactory solution [see (*2*)]? Although answers are beginning to emerge, there can be no meaningful discussion of this subject until we resist the impulse to assign blame. Nor can we hold to the simple belief that with willpower alone, one can consciously resist the allure of food and precisely control one's weight. Instead, we must look at the facts dispassionately and uninfluenced by the numerous competing interests that drive debate on this subject.

The facts are these: (i) The increasing incidence of obesity in the population is not reflected by a proportionate increase in weight; (ii) the drive to eat is to a large extent hardwired, and differences in weight are genetically determined; and (iii) obesity can be a good thing depending on the environment in which one (or one's ancestors) finds oneself. Progress toward an understanding of the gene/environment interaction that causes obesity will require the implementation of a broad-based clinical and basic research program.

In the past decade, the incidence of obesity increased by one-third from 23.3% in 1991 to 30.9% today (*3*). During this same interval, the weight of the typical American increased by an average of approximately 7 to 10 pounds (depending on a person's height) (*3*). Although none of us would, or should, take weight gain of this amount lightly, this difference is much smaller than the enormous variation in weight that can be observed in a cross section of the U.S. population in 2002. The fact that an incremental increase in the average weight has had a highly significant effect on the incidence of obesity is rooted in the definition of obesity. Obesity is diagnosed when weight normalized for height, or body mass index (BMI) (the weight in kilograms divided by the square of the height in meters), exceeds a defined threshold. People are said to be overweight if their BMI exceeds 25, and obese if their BMI exceeds 30. Above these BMIs, more or less, the health risks of an increased weight, or adiposity to be more precise, become increasingly evident (*4*). Because weight is distributed around a mean value in the population, an increase in the average BMI in the U.S. population from 26.7 to 28.1 (as above, 7 to 10 pounds) between 1991 and 2000 has led to a marked increase in the number of people with BMI $>$ 30 (*3*, *5*). Thus, because obesity is defined as a threshold, a relatively small increase in average weight has had a disproportionate effect on the incidence of obesity (Fig. 1). The effect of changes in the mean value for a trait on the frequency of disease is well established (*6*).

This analysis is not intended to minimize the importance of the fact that more than half of the U.S. population is now overweight or obese and that the environment has contributed to this public health problem. (In fact, this analysis could be viewed as good news, insofar as a relatively small achievable decrease in the average weight of our population could be of enormous public health benefit.) Rather, it is intended to highlight the fact that the change in weight attributable to any recent change in our environment, such as a change in diet or a more sedentary life-style, is much smaller than the enormous differences in weight, often numbering in the hundreds of pounds, that can be observed among individuals living in today's world (*7*). Thus, one might ponder why, in our current environment where almost everyone has essentially free access to calories, anyone is thin. The answer appears to reside in our genes and the way in which they interact with environmental factors.

Twin studies, adoption studies, and studies of familial aggregation confirm a major contribution of genes to the development of obesity (*8*, *9*). Indeed, the heritability of obesity is equivalent to that of height and exceeds that of many disorders for which a genetic basis is generally accepted (*8*). It is worth noting that height has also increased significantly in Western countries in the 20th century; for example, the average U.S. Civil War soldier was 5'4" tall. Yet, in contrast to the situation with obesity, most people readily accept the fact that genetic factors contribute to differences in stature. The critical contribution of genes to individual variation, and of environment to differences in populations, was framed by John Murray in an article reporting changes in BMI over time among students at Amherst College. Murray wrote, "In any individual's case, genetic factors play a role in determining body size but they tend to cancel out in large samples from a genetic pool, leaving levels and trends in body size that result from environmental factors" (*10*). The power of the genes that regulate weight is illustrated by the following case.

Four years ago, a 200-pound 9-year-old English girl, whose legs were so large she could barely walk, was found to lack the weight-regulating hormone leptin (*11*). Treatment with leptin dramatically reduced her food intake, and that of her similarly affected cousin, to the point where they both now have body weights within the normal range for their age and live normal lives (*12*). Before leptin treatment, the younger child consumed in excess of 1100 calories at a single meal, which is approximately half the average daily intake of an adult. With only a few leptin injections, this was reduced by 84% to 180 calories, the typical intake of a normal child (*13*). A number of other genes have now been causally linked to human obesity, and 5 to 6% of severely obese children have been shown to carry defects in known single genes (*14*–*17*). That there are likely to be other genetic forms of obesity is strongly suggested by the fact that 10% of morbidly obese children who do not carry mutations in known genes come from highly consanguineous (inbred) families (*13*).

In general, obesity genes encode the molecular components of the physiologic system that regulates energy balance [(*18*,

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19) and reviewed elsewhere in this issue]. This system precisely matches energy intake (food) to energy expenditure to maintain constant energy stores, principally fat.

That there must be a system balancing food intake and energy expenditure is suggested by the following analysis. Over the course of a decade, a typical person consumes approximately 10 million calories, generally with only a modest change of weight. To accomplish this, food intake must precisely match energy output within 0.17% over that decade (*20*). This extraordinary level of precision exceeds by several orders of magnitude the ability of nutritionists to count calories and suggests that conscious factors alone are incapable of precisely regulating caloric intake.

A key element of this homeostatic system is the hormone leptin, which is produced by adipose tissue and reports nutritional information to key regulatory centers in a brain region known as the hypothalamus. Increased body fat is associated with increased levels of leptin, which then act to reduce food intake. Mutations that result in leptin deficiency are associated with massive obesity in rodents and humans (*11*, *19*). A decrease in body fat leads to a decreased level of leptin, which stimulates food intake and reduces energy expenditure. Indeed, the reduced energy expenditure observed after dieting necessitates a disproportionately low caloric intake for the stable maintenance of weight loss (*21*). It is the activation of this potent behavioral and metabolic response to weight loss that makes successful dieting so difficult.

Overall, this homeostatic system can maintain weight within a relatively narrow range. Why then are some individuals obese and others not? It appears that the intrinsic sensitivity to leptin is variable and that, in general, obese individuals are leptin-resistant (*22*). Because of this, only a subset of obese people respond to leptin therapy with a significant amount of weight loss; the majority do not (*23*). The molecular basis for leptin resistance is not yet fully understood but is currently an area of intensive investigation.

The homeostatic system regulating energy balance induces a powerful drive to eat after a significant amount of weight has been lost. Feeding is a complex motivational behavior, meaning that many factors influence the likelihood that the behavior will be initiated. These factors include the unconscious urge to eat that is regulated by leptin and other hormones, the conscious desire to eat less (or more), sensory factors such as smell or taste, emotional state, and others. Key neural center(s) somehow process this diverse information. Although there is clearly cross-talk between the brain regions that produce the basic drive to eat and higher brain centers from which one might express the conscious wish to eat less, there is public disagreement about the relative potency of these often conflicting drives (as witnessed by the plethora of televised infomercials on diet plans) (*24*). Those who doubt the power of basic drives, however, might note that although one can hold one's breath, this conscious act is soon overcome by the compulsion to breathe. The feeling of hunger is intense and, if not as potent as the drive to breathe, is probably no less powerful than the drive to drink when one is thirsty. This is the feeling the obese must resist after they have lost a significant amount of weight. The power of this drive is illustrated by the fact that, whatever one's motivation, dieting is generally ineffective in achieving significant weight loss over the long term (*25*). The greater the weight loss, the greater the hunger and, sooner or later for most dieters, a primal hunger trumps the conscious desire to be thin. It should be noted, however, that modest weight loss—on the order of 10 pounds—has been achieved in some studies, and weight loss of this magnitude reduces the severity of diabetes and other conditions associated with obesity (*26*, *27*). Perhaps, in advance of a weight loss strategy superior to dieting, we should reduce our expectations.

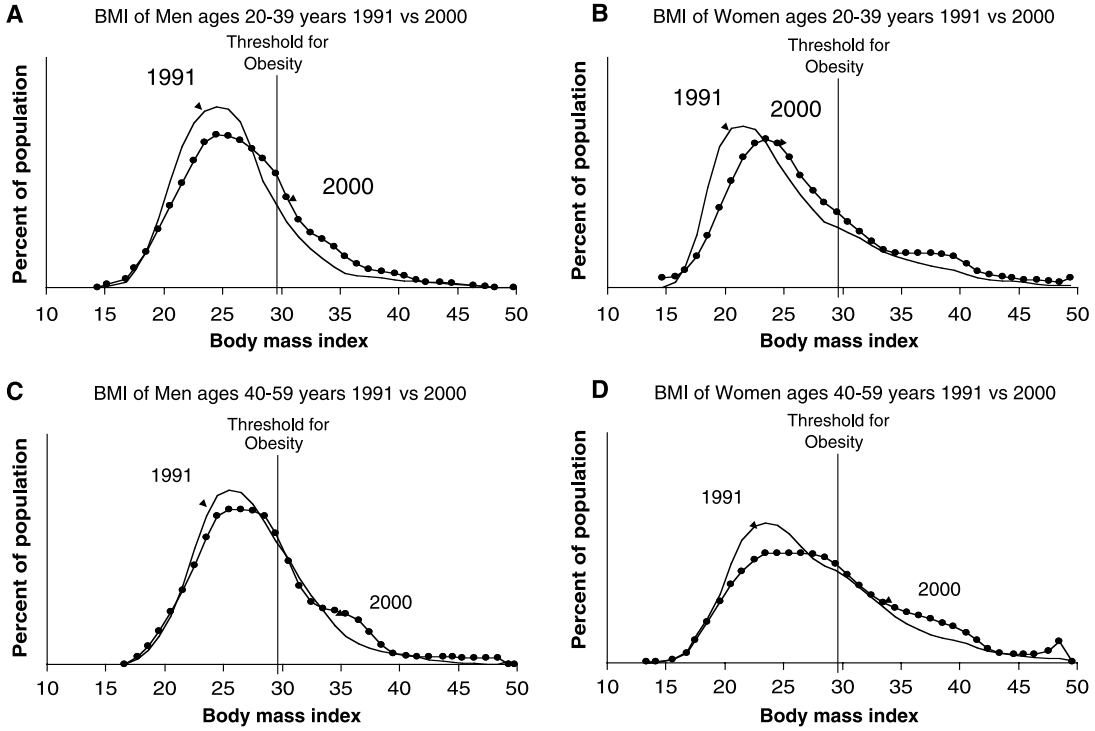

Fig. 1. The smoothed distribution of BMI for men and women in the United States aged 20 to 39 (**A** and **B**) and 40 to 59 (**C** and **D**) is shown for the years 1991 and 2000. In both cases, the distributions have shifted to the right and become more skewed. For the 20-to-39 age group, the average BMI for males increased from 25.9 to 27.0, and the average BMI for females increased from 25.4 to 27.5. For the 40-to-59 age group, the average BMI for males increased from 27.5 to 28.3, and the average BMI for females increased from 27.6 to 29. In both cases, there was a marked increase in the number of individuals with BMI > 30. At all ages, BMI is highly variable, with some individuals having a BMI > 45 and others having a BMI < 20, a difference that in some cases corresponds to hundreds of pounds. [Figures courtesy of K. Flegal]

What then is the role of the environment? As noted above, the increase in weight in our population is not evenly distributed; there has been a disproportionate increase in the number of massively obese people in recent years, especially in certain ethnic groups (*28*–*31*). Mean-difference analysis of this trend (Fig. 1) reveals that in recent years the BMI of U.S. adults in the lowest percentiles has not changed nearly as much as the BMI of those in the highest percentiles (*3*, *5*). Thus, in modern times, some individuals have manifested a much greater increase of BMI than others, strongly suggesting the possibility that in our population (species) there is a subgroup that is

genetically susceptible to obesity and a different subgroup that is relatively resistant.

The biologic system that regulates weight, although robust, is under intense selective pressure, and the genes that constitute it would be expected to vary depending on the environment. For people who lived in times of privation, such as hunter-gatherers, food was only sporadically available and the risk of famine was ever present. In such an environment, genes that predispose to obesity increase energy stores and provide a survival advantage in times of famine. This is the so-called "thrifty gene hypothesis" put forth by James Neel in 1962 (*32*). Indeed, thrifty genes could be imagined to be genes that lead to leptin resistance, the end result of which would be the efficient retention of nutrients as adipose tissue. Consistent with this idea is the finding that obesity and an increase of plasma leptin levels, indicative of leptin resistance, are characteristic of Pima Indians living a "Western" life-style, whereas Pima Indians living a more "native" life-style remain leaner and have low leptin levels (*33*).

For people descended from the inhabitants of the Fertile Crescent or, more recently, Western societies, the risk of starvation was markedly reduced by the domestication of plants and animals and the ability to store food (*34*). But these developments also exposed those who became obese to significant health problems. In this environment, selection against obesity might be expected. Some argue that because the health consequences of obesity generally affect people beyond childbearing age, genetic selection against obesity is not robust. However, an insightful article by Jared Diamond in 1992 suggests otherwise (*35*). Diamond pointed out that, among other things, obesity is associated with gestational diabetes, which has potentially deleterious consequences and would thus be strongly selected against. Gestational diabetes increases the risk of miscarriage and it can also lead to a cephalopelvic disproportion, an event that can have catastrophic consequences for both mother and child. Although the health complications of obesity are often not evident until later in life, it has also been shown that depriving children of the care and emotional support provided by their grandparents, especially grandmothers, has important consequences. A number of recent reports note the pivotal role of grandparents in gathering food for children and emphasize their critical role in the human social structure (*36*). In addition, increased adiposity is associated with an increased risk of predation in animals. Thus, in circumstances where the risk of starvation is reduced, one might expect genes that resist obesity and its complications to have a selective advantage. Such selection can, in principle, be quite rapid. As eloquently outlined by Jon Weiner in *The Beak of the Finch*, there is preexisting variation in all natural populations (*37*). As a consequence, natural selection can be observed in a single generation as nature weeds out the maladapted under changing environmental conditions, leaving the more highly adapted individuals to proliferate. Thus, rapid changes in population characteristics are generally the result of a gene/environment interaction.

Today, most people in Western societies have access to an abundance of food, and they lead a more sedentary life-style than did hunter-gatherers. However, as a species, we carry the genetic legacy of both environments. Might it be that it is the obese who carry the "hunter-gatherer" genes and the lean that carry the "Fertile Crescent" or "Western" genes? In support of this idea is the observation that populations that were historically most prone to starvation become the most obese when exposed to a Western diet and more sedentary life-style. This is true of the Pima Indians, Pacific Islanders, and many other high-risk populations (*29–31*). Thus, in modern times, obesity and leptin resistance appear to be the residue of genetic variants that were more adaptive in a previous environment. If true, this means that the root of the problem is the interaction of our genes with our environment. The lean carry genes that protect them from the consequences of obesity, whereas the obese carry genes that are atavisms of a time of nutritional privation in which they no longer live. [Some elements of this argument are an extension of the ideas in J. Diamond's brilliant book, *Guns, Germs, and Steel* (*34*).]

Once a molecular framework for the system regulating weight has been more fully developed, the next frontier will be the identification of the genes and genetic variants that cause obesity in humans. Enormous advances have been made, and the progress of the genome project will further accelerate such efforts. As more elements of this physiologic system are added, the impact of environment on their function will become better understood. An understanding of why obesity is associated with diabetes, heart disease, and hypertension is also needed. We also need to understand whether diets with different nutrient compositions have different effects on weight regulation. Still, patience is called for; scientific advances take time, and the translation of those advances into new treatments often takes even longer. The field of cancer research, for example, was invigorated by the elucidation of the molecular machinery that controls cell division. However, it was not until recently that this new molecular understanding was translated into entirely new types of therapy, such as the protein-tyrosine kinase inhibitor Gleevec, with more to come. Our approach to the obesity epidemic should be analogous: Identify the molecular components of the system that regulates body weight, define what is different about the system in lean and obese subjects, and elucidate how environmental and developmental factors alter the function of this system. Such a foundation is essential for the development of rational therapies. Substantial advances have been made, and it is a propitious time to discuss the need for a large effort aimed at understanding the biological basis of obesity.

In the meantime, a different kind of understanding is called for. Obesity is not a personal failing. In trying to lose weight, the obese are fighting a difficult battle. It is a battle against biology, a battle that only the intrepid take on and one in which only a few prevail.

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