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Weighing in on the lean genes.

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Research Article

Editorial

By now, it is a cliche to say that obesity has reached epidemic proportions in the United States and other Western countries. However, like many cliches, it is a fact. Epidemiologic studies have shown that a 20% excess in weight imparts a health risk, and, by this criterium of obesity, 20–30% of men and 30–40% of women are obese in the United States. Because of this high prevalence, and the morbidities associated with obesity, a great deal of work has been done on the pathologic manifestations, etiology, and treatments of obesity (1–4).

Simply put, obesity involves excess storage of food-derived calories as triglyceride in adipose tissue depots due to either excessive caloric intake, decreased caloric expenditure, or both. With respect to etiology, the debate has largely centered on issues related to nature versus nurture. In other words, to what degree is obesity genetically linked versus acquired due to various environmental factors (5)? Abnormalities on either side of the caloric balance equation could have a genetic or environmental component. Given the frequency with which obesity occurs, it seems highly likely that the etiology is heterogenous across a human population. Thus, environmental and genetic factors are probably both important, but the relative significance of each, or the interplay between the two, varies greatly among individuals.

The most widely subscribed theory for the etiology of obesity involves the set point concept (6). According to this notion, each person has an internal set point, or adipostat, allowing one to read the quantity of adipose tissue stores and then regulate these stores to an internal set point by modulating caloric consumption, physical activity, or thermogenesis. This would require a well regulated system with afferent and efferent arms and a signaling mechanism whereby information concerning adipose stores is provided to a sensing mechanism, presumably in the hypothalamus, which then adjusts the homeostatic process to maintain adipose stores within the proper range. An attractive model for such a regulatory system would hold that adipose tissue secretes a circulating factor whose blood concentration is in proportion to total adipose tissue stores, and the level of this factor is then sensed by a specific hypothalamic receptor; this signaling system is then tightly coupled to an afferent arm regulating caloric storage. Abnormalities in any of the components of this regulatory pathway could lead to obesity, and inherited defects could provide the genetic contribution to obesity.

Abundant evidence exists demonstrating the importance of environmental factors—witness the marked increase in obesity prevalence in Asian and Indian populations living in their native countries versus the United States. On the other hand, genetic influences are also clearly at play. This is easily demonstrated by examining the results from twin studies. When identical twins are reared apart, there is a remarkable concordance in the degree of adiposity, indicating that, independent of the environment, genetic factors control the degree of obesity within individuals (5).

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Much work has gone into dissecting the genetic components responsible for obesity. This has involved the search for "thrifty genes," genes which control appetite, spontaneous physical activity, sympathetic activity, and so on. Recently, this entire field received an enormous boost from the report of the cloning of the gene responsible for obesity in the *ob/ob* mouse (*ob* gene). Zang et al. (7) reported an elegant and important study in which they used a positional cloning strategy to identify the gene responsible for obesity in genetically obese C57BL/CJ *ob/ob* mice. The *ob* gene encodes a protein of 167 amino acids which is apparently exclusively expressed in adipose tissue. Sequence analysis indicates that this gene product is a secreted protein, consistent with the view that it provides a feedback signal related to the size of overall body adipose tissue stores. Importantly, when the sequence of the *ob* gene was compared in lean versus obese littermates, all the obese mice displayed a point mutation in codon 105 (CGA→TGA) changing the coding sequence of arginine to a stop codon. There was a corresponding increase in ob gene mRNA levels in the obese mice, suggesting that the non-sense mutation encodes a nonfunctional protein leading to the development of obesity. In a separate obese mouse model (7), the same authors found a complete absence of the *ob* gene, again suggesting that obesity ensues without a functional ob gene product.

Control of body weight is a complex process, and subtle regulatory changes can have a large impact. Assuming 1 lb of fat equals 3,500 kcal, a 100-kcal excess of energy intake compared with expenditure on a daily basis would lead to a 10-lb weight gain in the course of 1 yr. This is about the amount of calories in a slice of bread or the amount expended in 10 min of moderate exercise. The discovery of the *ob* gene is a major advance in understanding this regulatory system. The *ob* gene product is likely to be a circulating protein secreted as a reflection of adipose tissue stores and in response to nutritional influences. It may interact through a receptor mechanism with hypothalamic centers and function as a satiety factor to control eating behavior. Through hypothalamic efferent mechanisms, the ob protein could also influence thermogenesis, physical activity, and other aspects of energy balance. At this point in our understanding, it would appear that a deficiency of, or resistance to, the ob protein is strongly associated with the genesis of obesity.

Of course, mice are not men, and the exploration of this *ob* gene in human obesity has just begun. In this issue of *The Journal,* Considine et al. (8) have cloned the human homologue of the *ob* gene and provided its full-length sequence. More importantly, they have used a PCR method to analyze the entire coding sequence of this gene in a series of lean control and obese subjects. Unlike the case in the mouse, no mutations in the *ob* gene were found in their obese population. Interestingly, codon 105 (the site of the mutation in obese mice) is CGG in humans, meaning that two point mutations would be needed to change this to a stop codon. It should be noted that only a limited number of patients are included in the study by Considine et al. (8), and it remains possible that a small, but as yet unstudied, fraction of obese humans will display a functionally significant mutation in the *ob* gene.

This represents the first reported study of the *ob* gene in human obesity and, while it is a bit disappointing, it should not

be altogether surprising that the same mutation seen in mice does not appear in humans. After all, in humans, obesity is a quantitative trait covering a continuous spectrum, whereas in the *ob/ob* mouse, it is a dichotomous phenotype. Clearly, obesity is a heterogeneous disorder in humans, and it is unlikely that any single mutation will describe the entire genetic contribution to this disease. Although the current study did not observe alterations in the coding sequence of the *ob* gene in human obesity, it did find an increase in adipocyte ob mRNA expression level in direct proportion to the degree of adiposity. Thus, if the *ob* gene product regulates eating, energy expenditure, or both, then these findings suggest that obese individuals may be relatively resistant to the biologic effects of the ob protein. Assuming the ob protein is part of the afferent arm in a regulatory pathway controlling adipose tissue stores, then there are likely to be many steps in this pathway which could be the site of acquired or genetic defects resulting in excessive caloric storage. Based on the findings reported by Considine et al. (8), coding sequence mutations in the *ob* gene are unlikely to explain a sizable component of human obesity, as they do in the *ob/ob* mouse. Although this points out that the details of the pathogenesis of obesity are likely to differ between mice and humans, it remains likely that the regulatory pathway, of which the *ob* gene is one component, will provide a bountiful yield of causative factors explaining a sizable proportion of obesity in humans. This is an exceedingly important topic, and it is a certainty that an explosion of information on this subject lies just ahead. Coupled to this explosion is the hope that this new information will provide new therapeutic insights and treatments for this common disorder.

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