Toward Understanding the Genetic Basis of Human Susceptibility to Obesity: A Systemic Approach

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ETIOLOGY OF HUMAN OBESITY

Epidemiologic studies of the past decades have provided overwhelming evidence that the prevalence of obesity increases rapidly, often reaching epidemic proportions, in subsistence communities emerging into affluence (1). These transitions may occur within a generation, and hence are too rapid to be explained by changes in genetic make-up of the population. It is therefore tempting to blame gluttony and sloth as virtually the sole culprits in the pandemic of obesity that has occurred in environments where highly varied and palatable energy-dense foods have become accessible all year round and where physical activity demands are low. However, interpretations of data based on prevalences and trends can often suffer from what may be referred to as the phenomenon of “meaningless means” if interindividual variations are overlooked. Within any given environment that promotes excessive energy intake and discourages physical activity, a section of the population, often large, does not become overweight or obese. One can still propose that family, social, and cultural habits—clustered under environmental factors that include learned lifestyle behaviors—play a protective role against their “obesigenic” environments (2), but equally valid are the arguments that lifestyle effects and behaviors may also be inherited, thereby propelling us into the complex area of gene–environment interactions. For example, a genetic predisposition to select high-fat foods or to be sedentary will depend on the availability of such foods or the need to perform physical activities. Moreover, the prime cause of obesity cannot be attributed to excess food intake or to low physical activity alone, as it has repeatedly been shown that not all individuals become obese when experimentally overfed (3), and there are lean habitual high-fat consumers with an overall higher energy intake and lower physical activity level than low-fat consumers (4). It is therefore evident that the efficiency of the metabolic
machinery is not a constant; it varies in response to the plane of nutrition, and it varies among individuals.

**Role of Genes**

By far the most convincing evidence that fatness is heritable derives from adoption studies showing that identical twins have similar body weights and body fat, even when reared apart, and that adopted children tend to have body mass indices (BMI) and fat distributions that are better correlated with those of their biological than of their adopted parents (5–8). These associations have been followed by studies in twins and across families, showing a role for genotype in the interindividual variability in metabolic rate (9), and how a low energy expenditure may be a risk factor for excess weight gain both during growth (10,11) and during adult life (12). It would seem therefore that two conditions predispose to obesity: an ample supply of food and a genetic predisposition to accumulate fat. In subsistence environments, the genes that confer a high susceptibility to fatness may be expressed, but in the absence of sufficient food, obesity cannot occur. The trigger for the rise in obesity worldwide is certainly the environmental changes that favor overeating and low physical activity, but the extent to which a given individual within that population will actually develop or resist obesity resides in the interaction between his genetic makeup and the environment.

**Nature-Versus-Nurture Debate**

It is probably futile to try to separate the contribution of genes from that of the environment for a phenotype as complex as body weight, the regulation of which comprises a high degree of lifestyle behaviors vis-à-vis food intake and physical activity. How can we separate what is innate from what is learned when these factors are so intertwined? To quote the Swiss primatologist Hans Kummer, “It is as if we wanted to determine the relative contributions of the musician and his musical instrument in the melody! By contrast, if the melody changes, we can then legitimately raise the question about whether it is the musician or the musical instrument (genes or environment) which has changed.”

In the analysis of genes versus environment therefore the pertinent question is, “What is the percentage change in the variance of the phenotype that is contributed by genes and by the environment?” In this context, the “level of heritability”—which is often estimated as the fraction of the population variation in a given obesity phenotype that can be explained by genetic transmission (13)—is highly dependent on how the study was conducted, on the kinds of relatives upon which they were based, and on what was used as the obesity phenotype (BMI, % fat). One can also expect that these values will be altered if appropriate adjustments are made for the relation between adiposity and BMI across age, sex, and ethnic groups (14). Of the three main types of study—family, twin, and adoption—that have attempted to quantify the size of the genetic contribution to the variation in BMI, those conducted with identical twins and fraternal twins reared apart have yielded the highest heritability levels, with
values ranging between 60% and 85% of the variation in BMI. In contrast, adoption studies have generated the lowest heritability estimates of 20% to 35%, and family studies have generally found levels of heritability intermediate between the twin and the adoption study reports. Each design has its advantages and disadvantages and incorporates assumptions that may well be violated, with implications for the strength of the findings. Whatever the true values for heritability of fatness, however, it is undeniable that within any population in a given environment, individuals vary in the genetic makeup that renders them more prone or more resistant to obesity. Of central interest for public health and clinical medicine is how to pinpoint the genetic and metabolic basis for such susceptibility to fatness or leanness.

**THE SEARCH FOR OBESITY SUSCEPTIBILITY GENES**

The developments in DNA technology over the past decade, coupled with computerized bioinformation and biostatistics, have provided growing optimism that genes underlying susceptibility to obesity (commonly referred to as obesity genes) will soon be identified. Several approaches have been used, namely, variants in candidate genes, positional cloning of candidate chromosomal regions, linkage studies in families, and association studies using DNA from case and control designs or comparing genotypes in samples characterized by varying degrees of obesity.

**Candidate Genes**

Within a few years of the landmark cloning of the gene coding for the hormone leptin in the mid-1990s, most of the single-gene (monogenic) obesities in rodent models have been identified, and mutations with strong effects and associated with juvenile-onset morbid obesity in humans have been detected in the genes coding for leptin, leptin receptor, pro-opiomelanocortin, prohormone convertase-1, and melanocortin-4 receptor (15). Although each of these mutations is rare, they extend to 23 the list of obesity-related Mendelian disorders for which loci have previously been mapped (e.g., the Prader–Willi syndrome, the Bardet–Biedl syndrome, and the Wilson–Turner syndrome). In the search to identify genes of importance in the much more common forms of human obesity, the relevant sequence variation in many other genes implicated in the control of food intake, thermogenesis, or substrate metabolism has been screened, including that of genes coding for the β3 adrenoreceptor, the uncoupling protein in brown adipose tissue, and its homologs (UCP2, UCP3) in other tissues, neuropeptide Y receptors 1 and 5, tumor necrosis α (TNF-α), and PPAR-γ (peroxisome-proliferator-activated receptor), to name just a few (16). In most studies, the associations were found to be absent, and in the few where associations have been reported, they were relatively weak and clouded by the high probability of false positives.

**Linkage and Association Studies**

Several genetic linkage studies using a genome-wide scan approach in family studies have been completed in Mexican Americans, Pima Indians, a diverse population
of blacks and whites, French Canadian families, and French families. These have identified various major loci linked to obesity on chromosomes 2, 5, 10, 11, and 20, and these different quantitative trait linkages (QTLs) are believed to encode multiple genes of importance for susceptibility to obesity (17). Although the quantitatively most important locus in each of these genes is partly identified, it is not yet known exactly which genes and which mutations in the genes are associated with obesity. Those areas of the human genome will no doubt be subjected to further intense scrutiny to identify obesity susceptibility genes. However, as recently underlined by Ravussin and Bouchard (13), one must also recognize that linkages with weaker statistical significance may be important, particularly when replicated in other datasets. Genetic associations with a high level of significance \( p < 0.001 \) have also been identified for variants of a number of genes, including Na/K-ATPase \( \alpha_2 \) and \( \beta_1 \) with respiratory quotient, haplotypes of variants in the UCP1 gene and the \( \beta_3 \) adrenergceptor gene with weight loss, and the UCP2 gene with BMI or energy metabolism. However, none of these associations has proved to be the result of a mutation affecting the function or amount of a gene product. An annual update of the human obesity gene map is provided by the Quebec group (17). From association and linkage studies, it seems that putative loci affecting obesity-related phenotypes are found on all except chromosome Y of the human genome. The numbers of genes and other markers that have been associated or linked with human obesity are increasing very rapidly, and are now well over 200.

**Obesity Susceptibility Genes Versus Genes for Weight Regulation**

The general belief is that if genes are contributing to human susceptibility to obesity, they are doing so because of DNA sequence variation (or variations) affecting expression or function. However, the tremendous advances of the past few years— spearheaded by the identification of most of the monogenic obesities in rodent models—have been almost exclusively in the identification of molecules that play a role in the control of food intake, metabolic rate, or substrate metabolism and in adipose cell biology. While this progress is central for a better understanding of energy balance and weight regulation, there has been little or no progress with respect to the heritability of fatness. To quote Bray and Bouchard (18): “This is particularly striking when one realizes that there is not one single obese human being whose excess body mass and body fat can be explained by a-specific mutation in one of the genes exerting its effects in relevant energy balance pathways, with the possible exception of the mendelian syndromes, which characteristically exhibit obesity. But we knew that much before the cloning of the single-gene obesity mouse models.”

With the recent publication of the human genome, it is likely that the emphasis in research will be on a bottom-to-top approach (i.e., from genes to functions), with the objective of discovering the combination of genes and mutations that contributes most to the predisposition to human obesity. However, we believe that this approach, although most certainly extending the list of genes that play a role in the regulation of body weight, will not necessarily lead to the identification of the major obesity
susceptibility genes. In the light of the previously mentioned disappointments, the research strategies directed at understanding the genetic basis of human susceptibility to obesity need to be reconsidered, with more emphasis on a top-to-bottom approach (from functions to genes). This approach, however, requires that the routes from top to bottom be better defined.

A SYSTEMIC APPROACH

Perhaps a starting point in such a reconsideration of a top-to-bottom approach is to revisit the Darwinian arguments as to why the human genome could harbor genes that predispose such a large fraction of the population to obesity. We are often reminded that the human body was designed (in evolutionary terms) to cope with recurrent food shortage periods—that is, the “famine and feast” way of life that probably prevailed during most of mammalian evolution. The general belief, as Neel has emphasized in an update of his “thrifty genotype” hypothesis (19), is that it is variations in the genes that underlie these formerly adaptive homeostatic mechanisms for survival in an environment of intermittent food availability that constitute the genetic basis of human susceptibility to fatness in our present environment. In other words, those with a genetic make-up most conducive to survival in an environment of frequent periods of food scarcity are the most susceptible to obesity in modern affluent societies. Conversely, those capable of maintaining a lean body weight without conscious effort in these same obesigenic environments are likely to be those with a genetic make-up that would put them at greatest risk of being eliminated in an environment of food scarcity. In any top-to-bottom strategy for understanding the genetic basis of human susceptibility to leanness and fatness therefore, it is of central importance to understand what these adaptive homeostatic mechanisms that optimize survival are and how they operate. From a standpoint of system physiology, the questions could be translated as follows: What are the fundamental control systems that allow a human individual to utilize the body’s energy stores optimally so as to maximize survival during prolonged starvation? What are their commands and what are their specific functional roles? Furthermore, as it is also an equally high priority to reestablish these energy reserves whenever food availability increases, the questions also arise as to what the control systems are that allow the rapid rebuilding of the prestarvation capacity for survival.

Revisiting Classic Studies of Human Starvation: A Necessity

Progress in the area of human energetics and body composition regulation is, however, hampered by the need to conduct longitudinal studies of experimental starvation and refeeding. During these, food intake, metabolic rate, and body composition are documented before weight loss, and then at various points during the dynamic phases of weight loss and subsequent weight recovery. Furthermore, if a primary objective is to understand the normal physiology of weight regulation in response to starvation and refeeding, then those studies should focus on the response of healthy
normal-weight (nonobese) individuals to starvation. This is a difficult, if not impossible, task in adult humans—let alone in infants, children, or adolescents—mainly because of the ethical problems that such prolonged starvation studies would entail and the practical constraints associated with long-term compliance with experimental procedures. Fortunately, the classic studies of experimental starvation and refeeding that were carried out in healthy normal-weight volunteers from 1915 to 1950 (20–22) continue to provide an invaluable source of untapped data. The desire to gain a better insight into the regulation of body weight and body composition by reanalyzing these data in the light of more modern concepts of body weight regulation has become irresistible, as similar studies can no longer be performed in humans for ethical reasons. It is primarily for these reasons that we conducted a series of reanalyses of these classic studies of starvation and refeeding, with particular emphasis on data from the 32 male volunteers who participated in the Minnesota experiment conducted at the end of World War II (22). The results of these reanalyses, which use both statistical and numerical approaches (23–25), suggest that the formerly adaptive homeostatic mechanisms for optimal survival in an environment of famine and feast are embodied in three distinct autoregulatory control systems: the control of partitioning between protein and fat (the two main energy-containing compartments in the body), and two distinct control systems for adaptive thermogenesis. In one of these (Fig. 1), the efferent limb is primarily under the control of the sympathetic nervous system, the functional state of which is dictated by overlapping or interacting signals arising from a variety of environmental stresses, including food deprivation, deficiency of essential nutrients, excess energy intake, and exposure to cold or to infections; it is thus referred to as the nonspecific control of thermogenesis. The other is independent of the functional state of the sympathetic nervous system and is dictated solely by signals arising from the state of depletion of the adipose tissue fat stores; it is hence referred to as the adipose-specific control of thermogenesis.

Compartmenental Model

An overall integration of these autoregulatory control systems in the regulation of body weight and body composition during a cycle of weight loss and weight recovery is discussed with the help of a schematic diagram in Fig. 2. This diagram embodies the main finding that the control of body energy partitioning between protein and fat is an individual characteristic during weight loss and weight recovery (23), and takes into account the existence of these two distinct control systems for adaptive thermogenesis that can operate independently of each other (25,26).

During starvation, the control of partitioning determines the relative proportion of protein and fat to be mobilized from the body as fuel—the individual’s partitioning characteristic (Pc) being dictated primarily by the initial body composition. The functional role of the control of partitioning is to meet the fuel needs of the individual in such a way that the energy reserve component in both the fat and protein compartments (i.e., the part that can be lost without death or irreversible damage) would reach complete depletion simultaneously—a strategy that ensures the maximum duration
FIG. 1. Schematic representation for the two distinct control systems underlying adaptive thermogenesis during prolonged starvation and subsequent refeeding. One control system, which is a direct function of changes in the food energy supply, responds relatively rapidly to the energy deficit. Its effector mechanisms are suppressed early during the course of starvation, and upon refeeding they are restored relatively rapidly as a function of energy reavailability, and are activated further if hyperphagia occurs during refeeding. Because the efferent limb of this control system—which is primarily under sympathetic nervous system (SNS) control—is dictated not only by the dietary energy supply but also by a variety of other environmental factors such as diet composition, specific nutrient deficiencies, ambient temperature, psychological stress, and so on, it is referred to as the nonspecific control of thermogenesis. By contrast, the other control system has a much slower time constant by virtue of its response only to signals arising from the state of depletion/repletion of the fat stores. It is therefore referred to as the control system operating through an adipose-specific control of thermogenesis. From Dulloo AG (26).

of survival in a given individual during long-term food scarcity. Furthermore, the energy conserved resulting from suppressed thermogenesis is directed at reducing the energy imbalance, with the net result that there is a slowing down in the rate of protein and fat mobilization in the same proportion as defined by the partitioning characteristic of the individual. Indeed, the fact that the fraction of fuel energy derived from protein (i.e., the $P_{\text{ratio}}$) remains relatively constant during the course of prolonged starvation, albeit in normal-weight humans (27), implies that neither control system underlying suppressed thermogenesis is directed at sparing specifically protein or specifically fat, but at sparing both the protein and fat compartments simultaneously. During starvation therefore the functional role of both control systems underlying suppressed thermogenesis is to reduce the overall rate of fuel utilization.

During refeeding, the control of partitioning operates in such a way that protein and fat are deposited in the same relative proportion as determined by the partitioning characteristic of the individual during starvation, and this serves to reestablish the individual’s prestarvation capacity for survival during long-term food scarcity. Furthermore, the increased availability of food leads to the rapid removal of suppression upon the nonspecific (sympathetic nervous system mediated) control of
FIG. 2. Schematic representation of a compartmental model for the regulation of body weight and body composition during a cycle of weight loss (prolonged starvation) and weight recovery (refeeding). In this model, the two distinct control systems underlying adaptive thermogenesis—the nonspecific control and the adipose-specific control—are integrated with the more "basal" control of partitioning between the body fat and protein compartments, as determined by the partitioning characteristic (Pc) of the individual. (See text for details.) BMR, basal metabolic rate; SNS, sympathetic nervous system. From Duitto AG (26).
thermogenesis. By contrast, the suppression of the thermogenesis under adipose-specific control is only slowly relieved as a function of fat recovery, such that the energy that continues to be spared is directed specifically at the replenishment of the fat stores. The net effect—as previously demonstrated using both statistical and numerical approaches in our reanalysis of data from the Minnesota experiment (23)—is that fat is deposited in excess of that determined by the partitioning characteristic of the individual, thereby contributing to the disproportionate rate of fat relative to lean tissue recovery. This phenomenon is often observed—both in adults after severe weight loss due to food unavailability and disease, and in infants and children recovering from protein-energy malnutrition and growth arrest (28). An adaptive process that accelerates the restitution of the fat stores rather than diverting the energy saved toward compensatory increase in body protein synthesis (an energetically costly process) would have survival value in the ancestral famine-and-feast lifestyle. This is because, by virtue of the fact that fat has a greater energy density and a lower energy cost of synthesis/maintenance than protein, it would provide the organism with a greater capacity to rebuild an efficient energy reserve rapidly, and hence to cope with recurrent food shortages. Thus the functional role of the adipose-specific control of thermogenesis during weight recovery is specifically to accelerate the replenishment of fat stores whenever food availability is increased after a long period of food deficit and severe depletion of body fat stores. This provides an alternative way of surviving without hyperphagia.

PERSPECTIVES

Genetic Basis of Human Variability in Adaptive Thermogenesis

In addition to evidence in humans from the Minnesota experiment (25,26), and more recently from the Biosphere-2 experiment (29), the existence of an adipose-specific control of thermogenesis has direct experimental support from carefully controlled energy balance and body composition studies in animals, conducted in the phase of weight recovery after starvation or growth arrest (30,31). It can also be shown to operate independently of the functional state of the sympathetic nervous system (32). It is proposed that it operates as a feedback loop between the adipose tissue fat stores and the skeletal muscle, and would hence comprise a sensor of the state of depletion of the fat stores, a signal dictating the suppression of thermogenesis as a function of the state of depletion of the fat stores, and an effector system mediating adaptive thermogenesis in this skeletal muscle (26). To date, however, studies of prolonged starvation and refeeding have indicated that neither free fatty acids nor leptin in blood show temporal changes that correlate with the kinetics of suppressed thermogenesis under adipose-specific control (33), nor is there evidence that the uncoupling protein homologues, UCP2 and UCP3, have a physiologic role in the mediation of skeletal muscle thermogenesis (34,35). At present, the sensors, signals, and effector system of the adipose-specific control of thermogenesis remain unknown. Their discovery will no doubt have important implications for our understanding of body composition regulation, including the identification of candidate genes underlying the susceptibility to fatness.
In the meantime, the diagram in Fig. 2 provides a structural framework to explain the apparent paradox that suppressed adipose-specific thermogenesis that results in enhanced fat deposition during refeeding—and that is postulated to occur in the skeletal muscle—persists when the nonspecific control of thermogenesis is activated in organs and tissues recruited by the sympathetic nervous system (e.g., liver, kidneys, and brown adipose tissue). Such differentially regulated control systems for thermogenesis may have arisen during the course of mammalian evolution in order to satisfy the need for energy conservation directed specifically at the rapid recovery of body fat under a variety of environmental stresses, when sympathetically mediated activation of heat production has equally important survival value. Examples of the latter include thermoregulation during weight recovery in cold environments, the generation of fever during exposure to infections, and the concomitant enhancement of thermogenesis during weight recovery on a poor diet (e.g., one that is low in protein). In this case an excess energy intake—resulting from the consumption of large quantities of the poor diet in an attempt to meet the requirements of the specific nutrients—needs to be dissipated as heat (diet-induced thermogenesis [DIT]) in order to avoid excessive weight gain.

A recent reanalysis of human overfeeding experiments by Stock (36) showed that humans seem to possess a much larger capacity for DIT than is generally recognized. Although this capacity is poorly recruited on well-balanced diets, it is much more pronounced on diets poor in essential nutrients. In this context, Stock proposed that DIT may have evolved as a mechanism for regulating the metabolic supply of essential nutrients (protein, minerals, vitamins), with only a secondary role in regulating energy balance. Our own reanalysis of the human overfeeding studies revealed the strong possibility that relatively small individual differences in DIT on balanced normal-protein diets are amplified by protein-deficient diets (37). As shown in Fig. 3, the extent to which the mechanisms underlying DIT are recruited would seem to be a function of both the individual (as judged by the interindividual variability within each diet group) and the dietary protein level, the recruitment for DIT being weak on normal-protein diets but pronounced on low-protein diets. As even small interindividual variations in the efficiency of weight gain (and hence of thermogenesis) on well-balanced diets can, over months and years, contribute to weight maintenance in some and obesity in others, the possibility arises that overfeeding low-protein diets could serve as a tool for maximizing DIT, so exaggerating individual differences in energetic efficiency. In other words, low-protein overfeeding may serve as a “magnifying glass” for unraveling the genetic and metabolic basis whereby variations in thermogenesis contribute to susceptibility to leanness and fatness during overconsumption of the typical (well-balanced) diets of our affluent societies (36,37).

Genetic Basis of Human Variability in Energy Partitioning

Apart from variability in thermogenesis, it is clear that interindividual variability in the control of partitioning between protein and fat can also contribute importantly to human susceptibility to fatness. It is indeed well established, though not often
FIG. 3. Unmasking of interindividual variability in thermogenesis by low-protein overfeeding. The data represent the energy cost of weight gain (excess MJ consumed per kg weight gained) during 3 to 4 weeks of overfeeding in five volunteer subjects (Nos. 27, 28, 30, 33, and 34) who participated in both normal-protein (15%) and low-protein (3%) overfeeding in the gluttony experiments of Miller and coworkers (38,39). The two horizontal broken lines (enclosing the shaded area) correspond to predicted energy cost of weight gain on the assumption that weight gain is either 100% fat (45 MJ/kg) or 60% fat (30 MJ/kg), the latter value including cost of fat-free mass gain. The greater the deviation from the predicted values, the greater the likelihood that the excess energy was dissipated through enhanced diet induced thermogenesis (DIT). ME, metabolizable energy. From Dulloo AG (37).

appreciated, that the extra weight gain during the development of obesity reflects an increase not only in adipose mass (i.e., fat) but also in lean tissue (protein), and that the composition of the excess weight gained is a variable (40). Consequently, for the same surplus of food energy, an individual with a low partitioning characteristic will gain less protein and more fat than an individual with a high partitioning characteristic, which favors body protein deposition.

The importance of genotype in such partitioning between protein and fat has been demonstrated in the responses of 12 pairs of identical twins to experimental overfeeding, during which they all consumed an excess of 1,000 kcal/d, 6 days a week for a period of 3 months (41). Although mean weight gain was 8 kg, it ranged from 4 to 13 kg, and 37% of the variation in weight gain was associated with energy partitioning, assessed as the ratio of fat mass to fat-free mass. The mean value for this dimension of energy partitioning was 2:1, but it varied from 1:2 to 4:1 among the 24 individuals. In addition, the variance in response was at least three times greater between twin pairs than within pairs for gain in body weight and body fat. This therefore provides strong evidence that there are inherited differences not only in body weight and BMI, but also in the composition of the weight gained in response to overfeeding. A tendency to gain fat or lean tissues—that is, variability in their partitioning
characteristics—seems to be a major genetically determined factor in the susceptibility to obesity. These observations underscore the need for a better characterization of interindividual variability in energy partitioning, particularly in the area of susceptibility to fatness during the growth process.

Clues to the primary determinants of such variations in energy partitioning may also be derived from our reappraisal of the physiology of human starvation, where the interindividual variability in the control of partitioning between protein and fat during weight loss and weight recovery has now been reasonably well characterized. It has been shown that this is primarily determined not only by the prestarvation ratio of fat to fat-free mass (i.e., by the initial percentage of fat [Fig. 4]), but also by the size of energy reserve fraction in the protein compartment ($r_p$)—the fraction of the protein compartment that could be lost without death or irreversible consequences.

**FIG. 4.** Linear relation between the initial body composition (FAT$_0$, fat mass; FFM$_0$, fat-free mass) and the composition of weight loss ($\Delta$FAT: $\Delta$FFM) among the normal-weight men subjected to 24 weeks of semistarvation in the Minnesota experiment ($N = 31$; $r^2 = 0.7$, $p < 0.001$). The data for $\Delta$FAT: $\Delta$FFM are the values for change in body fat and FFM over the entire 24 weeks of semistarvation. The data for FAT$_0$/FFM$_0$ (range 0.06 to 0.34) follows a normal distribution, with a threelfold variability between the 10th and the 90th centile values (range, 0.08 to 0.26). For the regression, the 95% confidence intervals are within the inner dotted lines, whereas the predictive intervals are within the outer dotted lines. The significance of the overall linear model is high (F value, 55.5; $p < 0.001$) with a significant slope ($b$) of 2.29 (SD 0.31) ($p < 0.001$) and a nonsignificant constant intercept ($a$) of 0.078 (SD 0.055). The broken diagonal line represents the line of identity between the two ratios. This relation constitutes a cardinal feature that led to the construction of a mathematical model for predicting the partitioning characteristic ($P_c$) of an individual during starvation (42). According to this model, the $P_c$ has only two determinants: the FAT$_0$/FFM$_0$ ratio (which is essentially the initial percentage of fat) and $r_p$ (which is the protein reserve fraction ($r_p$)—that is, the fraction of the protein compartment that could be lost without death or irreversible consequences). From Dulloo AG (42).
**FIG. 5.** Histograms showing frequency distribution for the protein reserve fraction ($r_p$) of the men volunteers from the Minnesota experiment (22). The values of $r_p$ are calculated using a mathematical model for studying interindividual variability in fuel partitioning during starvation (42). A normal curve is superimposed over the histogram for comparison. Although the data $r_p$ appear skewed, the application of the Wilk–Shapiro/Flusk test normality statistical test shows that this variable could conform to a normal distribution, with Wilk–Shapiro value of 0.80. If the two possible outliers ($r_p$ values $> 0.5$) are omitted, the Wilk–Shapiro value is improved from 0.80 to 0.95. From Dulloo AG (42).

(42). The application of a mathematical model for predicting the partitioning characteristic of an individual during starvation (42) to the Minnesota data on the changes in body composition during weight loss showed that there was a large—at least twofold—variability in estimates of $r_p$ among the Minnesota men (Fig. 5). Future studies would need to explore whether interindividual variability in $r_p$ resides in the relative proportion of organ (visceral) mass to skeletal mass, in the fiber or biochemical composition of the skeletal muscle, or in variability in skeletal muscle metabolism. Whatever the phenotypes by which this large variability in $r_p$ expresses itself, it is likely to contribute in an important way to genetically determined variability in lean-to-fat tissue deposition, whether during weight gain in adults or during the growth process across infancy, childhood, and adolescence.

**CONCLUSIONS**

It is our contention that the origin of the genetic basis of human susceptibilities to fatness and leanness, most certainly polygenic, resides primarily within the three control systems that constitute the most important formerly adaptive homeostatic mechanisms in a hunter-gatherer or subsistence-farmer lifestyle of famine and feast. They probably conferred varying capacities to defend the body's protein and fat stores in an ancestral lifestyle of recurrent periods of food scarcity but now underlie our varying susceptibilities to fatness in a world where palatable foods are abundant all year round. Our understanding of the genes controlling them will depend upon the extent
to which these systems can be studied in isolation from each other, let alone from all kinds of environmental or pathophysiologic disturbances. The greatest challenges nowadays are therefore to find or design the experimental conditions most likely to unravel the molecular physiologic processes underlying each of these control systems.

The components of the control system underlying the adipose-specific suppression of thermogenesis—namely its sensors, signals, and effectors—can certainly be studied in isolation from the other control systems regulating body composition, but within the type of constraints that can only be imposed in animal experimentation.

Subtle differences among humans in their capacity for nonspecific control of thermogenesis in response to diet (i.e., in diet-induced thermogenesis)—while of quantitative importance in their different susceptibilities to obesity when cumulated over months or years—are unlikely to be picked up by conventional techniques during the relatively short durations of human experimentation. It may prove necessary to simulate the appropriate unbalanced dietary conditions (i.e., low-protein overfeeding) under which diet-induced thermogenesis is recruited to unmask some of the genetic and metabolic machinery responsible for human variability in thermogenesis.

Finally, in our pursuit of a better understanding of the determinants of susceptibility to obesity in childhood and adolescence, it is necessary first to understand the determinants that underlie interindividual variability in the partitioning between protein and fat during growth.

To reach these objectives, there are no alternatives except robust analysis of data on changes in body composition during longitudinal studies. In this context, the application of adequate statistical or numerical approaches that allow linearization of the relation between lean and fat tissues during growth—while taking into account the synchronization between the changes in height, muscle mass, and the mass of vital organs—is certainly a vital prerequisite.

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REFERENCES


DISCUSSION

Dr. Anantharaman: Based on your model, what do you feel would be the ideal micronutrient profile of a food used to refeed an infant who has been starved or malnourished?

Dr. Dulloo: At the moment, we don’t really know the answer. There is a real need for experiments to study those specific components that seem to conserve energy and to accelerate fat deposition. In the study by Ancel Keys—which is the closest one that can get to the normal physiologic situation without infection—they used a diet that was very low in fat, less than 20%, and still saw an acceleration of fat deposition (1). In animals we know that if you give a high-fat diet, you exacerbate this phenomenon even more. We have tried different dietary compositions—polyunsaturated fats, fish oil, n-6, n-3, and so on—and we can reduce the exacerbation of fat deposition a little but cannot eliminate it. The next thing will be to look at zinc and other specific micronutrients, but this hasn’t been done yet.

Dr. Vauy: You concentrated mainly on the genetics of food intake and fuel partitioning, but there are also the genes responsible for adipocyte differentiation and adipogenesis. Could you comment on that aspect?

Dr. Dulloo: I described the fundamental control systems where there may be strong genetic variability. We need to look at each of these. Would adipocyte differentiation, by whatever genes it may be mediated, be under the control of partitioning, be under the control of what we might call nonspecific thermogenesis, or be related to the suppression of thermogenesis that accelerates fat deposition specifically? We have to look at all these possibilities.

Dr. Shen: Could you give us your view on future genetically based treatment for obesity—for example, the use of gene therapy to intervene in obesity?

Dr. Dulloo: Everything is moving so fast that it is hard to foretell what is going to happen. We have problems just following the literature. Between the time I got the invitation to come here and now, at least six potentially very important obesity genes have been discovered. If you just look at intermediary metabolism, any of the enzymes in this enormous network has a potential candidate gene. Whether or not gene therapy could be applied, there are bounds to be ethical concerns. Are we going to treat half the world where people are becoming obese?

Dr. Robinson: Is there a method available for looking at differential gene expression in response to manipulations in the environment, such as diet and activity? In other words, are researchers looking at gene expression in response to environmental manipulation as opposed to genes associated with different levels of obesity or physiologic states?

Dr. Dulloo: These are very expensive studies and require the characterization of physical activity in an enormous number of subjects. I don’t know if anybody is doing this, but it’s a difficult task to monitor activity in thousands of subjects, and then to look for genetic difference. I agree it would be the ideal approach, but perhaps not feasible.

Dr. Robinson: I was thinking more about experimental manipulation of activity, diet, or other environmental factors—so you would exercise and then look for variations in gene expression.
Dr. Dulloo: It is highly probable that people are doing such studies but I am not personally aware of any.

Dr. Gortmaker: My understanding of your presentation is that it was mainly focused on diet processing and the genetic influences. What about genetic influences on more fundamental physical activity levels? I tend to think of us as being programmed to want to sit still unless we’re threatened with death, and then we may start running around! Do you have any sense of how one might partition the genetic influences into these two areas, energy intake versus energy expenditure?

Dr. Dulloo: It is futile to try to separate the effects of genes from environmental effects per se. Take the example of a musical performance. There are two parts to that—the person playing the music and the instrument. By just hearing the music, we cannot separate the contribution of the instrument from the contribution of the player. All we hear is the interaction of the two. In the end, we always deal with interactions.

Dr. Gortmaker: What I meant was that you spoke about dietary intake but not really about levels of physical activity in individuals, or the genetic basis of that physical activity. To what extent is that an important area for ongoing research?

Dr. Dulloo: It’s likely to be a very important area. The best reason I can give for that is the study of overfeeding done by Levine in the United States (2). He overfed his subjects and there was tremendous variability in weight gain in response to the same excess energy intake. The explanation for this did not lie in differences in BMR or the thermogenic response to meals, so they concluded that the effect was caused by an increase in activity not detectable by accelerometers or pedometers—in other words, fidgeting or low-level unstructured activity. This must have a very important genetic component. What drives one person to do more of this would be an interesting area to look for gene and environmental interactions.

REFERENCES