The Phenotype of Human Obesity: The Scope of the Problem

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Abstract

The prevention and treatment of childhood obesity have proven to be extremely difficult problems. Since the equation for maintaining energy balance is an extremely simple one, having only two terms, ‘energy in’ and ‘energy out’, the difficulties encountered in its application for obesity management are not immediately obvious. Among the problems that make practical application of the energy balance equation more difficult than expected are: (1) the precise feedback control system that is designed to maintain weight within a given range; (2) the aggressive resistance of the system to attempts to exceed its boundaries; (3) inaccurate assessment of energy intake in practice; (4) the dominant role of genes in determining body weight; (5) the polygenic nature of obesity and the fact that any single gene accounts for a small fraction of the genetic variation in weight; (6) underestimation of the genetic contribution to the current ‘epidemic’ of obesity; (7) the fact that ‘modifiable’ risk factors may be less modifiable than expected; (8) appreciation that family role modeling may be less influential than anticipated, and (9) the realization that our knowledge about the development of physical activity behaviors in childhood is extremely limited.

Introduction

Obesity is the most prevalent form of malnutrition in the developed world. At first glance, one might imagine that obesity should be a relatively simple condition to correct. After all, the energy balance equation has only two terms. Thus:

\[
\text{Dietary energy intake} - \text{Energy expended in activity} = \text{Body fat stored}
\]

In theory, then, one has merely to reduce the amount of energy consumed in food and/or increase the amount of energy expended in daily activities and the problem is solved. Moreover, the tool necessary to measure the primary endpoint...
variable, body weight, is simple, readily available, and easy to interpret – namely a reliable scale. Likewise simple, readily available and easy to interpret are the tools necessary to measure the secondary endpoint variable, body fat distribution. These are a tape measure and mirror for assessing body fat distribution. Nevertheless, both treating established obesity and preventing the development of obesity have proven almost intractable in practice. Why is this so? The answer is not simple. If it were, we would not be in this predicament. The plausible, proximate explanations lie in the fact that there are significant problems that confound a straightforward application of the energy balance equation.

**Problem No. 1**

*Man has evolved an exquisitely sensitive and precise feedback control system to maintain body weight within a genetically set range* [1–8]. Because an effective body mass is critical to survival, during the course of human evolution, man has developed an exquisitely sensitive and precise system for assessing the status of body energy intake and fuel stores [1–5] and for maintaining body weight within a relatively narrow range [6–8]. It is now abundantly clear that both gut and adipose tissue are in constant communication with the brain via the hormones cholecystokinin, ghrelin, glucagon-like peptide-1, peptide YY, enterostatin, bombesin, oxyntomodulin, secreted by the gut, insulin release by the pancreas and leptin released by adipocytes. Insulin and leptin signal the magnitude of fat stores and leptin inhibits neural pathways that stimulate food intake while promoting pathways that reduce feeding [6–8]. Ghrelin stimulates appetite, while the remaining hormones provide satiety signals [1–5]. Correspondingly, the brain responds with the appropriate efferent hormonal signals that regulate food intake and energy expenditure [6–8]. Thus, neuropeptide-Y and Agouti-related peptide stimulate eating while the pro-opiomelanocortin-derived peptides α- and β-melanocortin-stimulating hormones reduce eating [6–8]. When one attempts to reduce body weight, there is increased secretion of ghrelin, neuropeptide-Y and Agouti-related peptides, accompanied by a decreased release of leptin, insulin, and pro-opiomelanocortin. Further, sympathetic nervous system tone decreases and less thyroxine is converted to triiodothyronine, the active thyroid hormone [6, 7]. The net result of these changes is that energy expenditure declines [6, 7]. That this resistance is operative and effective in man has been amply demonstrated by rigorous clinical investigation. Leibel et al. [7] demonstrated that a weight reduction of 10% was accompanied by a decrease in total daily energy expenditure in the order of 6–8 kcal/kg of fat-free mass.

**Problem No. 2**

*The system conspires against our attempts to exceed its boundaries.* While it is well known that obesity results in peripheral resistance to the
actions of insulin, it is less well appreciated that the hypothalamus in obese individuals also develops a resistance to the actions of leptin. While it is not entirely clear whether the leptin resistance develops in cells that respond directly to leptin itself or in cells that are further ‘downstream’ of leptin’s proximate action, the overall result is that leptin’s role in reducing food intake is blunted [8].

In consort then, the overall effects of Problem No. 1 and Problem No. 2 are to increase the difficulty of losing weight since there is an effective ‘hormonal resistance’ to attempts to diminish body mass by reducing energy expenditure and by reducing the break on satiation [6–8]. In clinical practice, the net result is that the involuntary, long-term, biological regulatory system outlasts the voluntary, short-term response system of human compliance and perseverance.

Problem No. 3

We do not have practice tools that will let us know confidently which term in the energy balance equation is the culprit in any individual circumstance. The long-established tools of direct and indirect calorimetry, including the doubly labeled water method, are extremely accurate and very precise by any usual standard of methods applied to human physiology. Thus energy expenditure can be measured to a precision of about ±2–5% [9, 10]. However, a long-term, daily energy excess of 2–5% is greater than that necessity to result in a significant degree of obesity.

Tools to measure energy intake, on the other hand, are notoriously inaccurate. Trabulsi and Schoeller [11] compared multiple conventional approaches to assessing dietary intake in humans with unbiased estimates of actual intake derived from simultaneous measurement of total daily energy expenditure using doubly labeled water. Conventional methods of dietary assessment regularly and significantly underestimated actual energy intake by about −20% on average [11]. In the context of maintaining energy balance, an inaccuracy of 20% is a truly gargantuan amount. In practical terms, this means that, except under conditions of gross over-consumption, dietary intake data are not sensitive enough to permit confident conclusions about the role of modest increments in energy intake as a contributing factor in the development and/or maintenance of obesity in individuals.

Problem No. 4

Our genes account for a greater fraction of the variance in body weight than all other physiological, biochemical, and behavioral variables combined. Body weight is largely determined by genetics. Long-term
and well-established studies carried out in many thousands of twin pairs have confirmed that genes are responsible for 50–90% of the variance in BMI [12]. Consensus overall estimates derived from such twin studies estimate that about two thirds to three quarters of the variance in BMI distribution in populations is the result of genetics. Likewise, genes are a major contributor to body fat mass, fat distribution, energy intake, and responses to alterations in energy intake and diet composition [13–15].

Table 1. Human obesity gene map

| 1 | The Y chromosome is the only chromosome without a putative obesity locus |
| 2 | More than 250 quantitative trait loci for body weight have been identified in more than 60 genome-wide scans |
|   | The FTO gene has been the most consistently observed gene associated with the common form of human obesity |
| 3 | More than 125 candidate obesity genes have been identified |
|   | More than 20 of these are supported by findings from 5 or more separate studies |
| 4 | Fifty obesity-related syndromes have been mapped |
|   | Causal or candidate genes have been identified in most of these syndromes |
| 5 | More than 175 cases of human obesity have been shown to be due to more than 70 single mutations in 11 genes (monogenic obesity) |
|   | The vast majority of these are mutations in the melanocortin-4 receptor gene, accounting for the obesity observed in approximately 90% of the people who have been found to have monogenic causes of obesity |

Adapted from Rankinen et al. [16].

Problem No. 5

The common form of human obesity is a polygenic disorder in which many genes contribute to the body weight phenotype and each gene contributes only a small fraction of the variance. Table 1 shows the status of the human obesity gene map at the end of 2005 [16]. All chromosomes but the Y chromosome house genes with loci that contribute to body weight. In syndromes that have obesity as part of their phenotypes, more than 50 loci have been mapped and causal or candidate genes have been identified in most of these [16]. However, as a rule, the identified genes have not provided a mechanism for the development of obesity.

For the forms of obesity commonly present in the general population, more than 250 quantitative trait loci have been identified in more than 60 genome-wide scans (table 1). From such scans, genetic variants in the FTO gene have now been most consistently identified as the most important contributors to common obesity phenotypes [17–20]. Individuals with at-risk
FTO haplotypes ‘yield a proportion of attributable risk of 22% for common obesity’ [18], weigh ‘about 3 kg more’ [19], have a ‘1.67-fold increased odds of obesity’ [19] and are, ‘on average, 1.0–3.0 BMI units heavier’ [17] than those who do not have the at-risk haplotypes.

More than 70 mutations in eleven genes have now been identified as monogenic causes of human obesity [16] (table 1). As opposed to the case of the genes in obesity syndromes, the genes identified as monogenic causes of obesity do provide clear mechanisms for the obesity phenotype. The majority of these genes account for only a very few obese individuals [21, 22]. One, however, represents a significant contributor to human obesity. Loss of function mutations in the melanocortin-4 receptor gene have been identified in 2–5% of individuals with childhood onset obesity [23–25].

Nonetheless, the majority of the other candidate genes [16] have not been demonstrated to contribute individually to a significant fraction of the variation observed in body weight. Thus, for example, Masud et al. [26] reported a meta-analysis of the relationship of PPARγ polymorphisms and BMI in more than 19,000 individuals, showing that the polymorphism effect size was less than one BMI unit. Similarly, a meta-analysis of the association of β3-adrenergic receptor gene polymorphisms with BMI in more than 6,000 persons demonstrated a gene variant effect on BMI of only 0.3 BMI units [27].

**Problem No. 6**

The common refrain that genes are not contributing to the current obesity ‘epidemic’ is oversimplified. Because the prevalence of obesity has more than doubled over the last several decades and because gene variations due to environmental evolutionary pressures do not occur on this time scale, genetic contributions to the current problem are often dismissed. This is not an entirely defensible position. First, Helmchen and Henderson [28] presented evidence that the increase in population BMI actually began more than a century ago. The prevalence of obesity in the early 1880s in 40- to 59-year-old adults was less than 2%. At the end of the 19th century, the prevalence was nearly 5% [28]. Thus, like the doubling of obesity prevalence that has taken place in the final two decades of the 20th century, there was also a doubling of the prevalence of obesity in the last two decades of the 19th century. However, since the absolute prevalence was low a century ago, there was little notice and less public health concern. Nonetheless, a century is still a trivial time period on the evolutionary scale required for changes in the DNA of the population.

In order to further appreciate why an individual’s genotype remains an important consideration in the modern obesity ‘epidemic’, it is first necessary to understand that the term ‘heritable’ defines the proportion of the
The twin studies discussed above demonstrate that the majority of the shape of the bell-shaped distribution of BMI is due to genes within the population. In an environment where there is little food and where a significant amount of energy must be expended to obtain the food (human hunter-gatherer prehistory, for instance), the shapes of the ‘genetic’ body weight distribution curve and of the phenotypic ‘actual’ body weight distribution curve are the same, but the observed phenotypic distribution itself is shifted to the left (thinner). Conversely, in an environment such as that which exists in developed countries today, where food is available in excess and physical activity is minimized, the shape of the ‘genetic’ body weight distribution curve has not changed from that found in prehistoric times. However, the ‘actual’ observed phenotypic distribution of body weight has shifted to the right (fatter). In other words, genes have not changed and still account for the majority of the distribution variance, but the measured body weights themselves have moved into the obese range. Support for this right-shifting position comes from established population measurements in the United States demonstrating that children who are at the upper end of the body weight distribution curve are becoming fat faster than those in the middle of the distribution [29].

An additional reason not to ‘count out’ a genetic contribution to the current obesity ‘epidemic’ is the fact that while genes themselves may not have changed, the distribution of gene frequencies within the population may have been altered by influences such as assortative mating due, for instance, to obese individuals being more likely to marry other obese individuals or, conversely, to thin people being less likely to marry obese people. Redden and Allison [30] demonstrated that this is not a trivial consideration in altering the prevalence of obesity across several generations of matings. Likewise, Speakman et al. [31] demonstrated convincingly that assortative mating exists for obesity by directly determining adiposity using DXA. Moreover, social ties may contribute to this phenomenon because obesity has been shown clearly to spread within social networks [32, 33].

**Problem No. 7**

The traditional therapeutic paradigm that tends to minimize ‘non-modifiable’ risk factors and focus on ‘modifiable’ risk factors may be flawed by the fact that many ‘modifiable’ risk factors may not be so modifiable after all. Most conventional approaches to obesity treatment tend to minimize the ‘non-modifiable’ risk factors such as genes, gender and age, while focusing on ‘modifiable’ risk factors such as eating habits and physical activity behaviors. In this context, considerable discussion has focused on the environmental factors [34] and on societal policies and processes [35] that might be
modifiable and alter the development, progression, or treatment of obesity. In pediatrics, particular attention is paid to early infancy where common logic has it that, since children who gain weight rapidly in early infancy are more likely to be obese later, we can successfully prevent obesity by intervening during this ‘modifiable’ window of opportunity by, among other measures, altering dietary intake and fostering healthful dietary eating behaviors.

Nonetheless, this window of opportunity may be less modifiable than anticipated. The genetic contribution to rapid growth during the first 2 years of life is substantially more than is commonly appreciated [36]. Heritability is by far the principal determinant of weight from birth to 3 years of age and is the major contributor to the change in body weight Z score from birth to 6 months of age, from birth to 12 months of age and from birth to 24 months of age [36]. Moreover, we are beginning to identify the genes responsible for rapid weight gain in childhood [18, 19, 37].

Likewise, childhood eating behaviors might not be as modifiable as commonly proposed. Thus, for example, Fisher et al. [38] recently demonstrated significant heritability contributions to eating behaviors in overweight Hispanic children and a genome-wide scan has identified a significant genetic linkage with the appetite-stimulating hormone, ghrelin [39]. Additionally, animal studies have shown that leptin signaling during the developmental period in which hypothalamic feeding circuits are ‘hard wired’ in mice permanently alters these circuits in adult mice [40, 41]. Likewise, oral leptin availability during lactation in rats can prevent the development of adult obesity when the animals are fed high-fat diets [42]. If similar phenomena exist in human infants, once CNS appetite and satiety circuits are ‘hard wired’ during early infant and childhood development, they may be effectively ‘immune’ to behavioral modification in later childhood and adolescence. Some evidence that eating behaviors are developed very early comes from studies showing that children as young as 2–3 years of age, like adults, already over-consume food when presented with large portion sizes and that these actions lead to excess energy consumption [43, 44].

**Problem No. 8**

*Modeling the family environment may not be as effective as commonly believed.* There is no question that parents influence the eating behaviors of their children [45]. However, the net effects of such influences on the eating behaviors of the child are complex and influenced by parenting styles [45, 46]. Although the family environment is commonly viewed as a shared environment for the family’s children, individual children often are subject to different (non-shared) aspects of this environment. Keller et al. [46] have shown that whether or not maternal feeding practices are shared or non-shared components of the home environment depends on the specific
feeding domain being measured’. This is particularly important since ‘behavioral genetic studies … suggesting that the environmental experiences that make children vary in weight status are primarily those that differ among children in the same family’ [46]. Thus, in this context, weight concerns, restrictive feeding practices and pressures to eat were unshared environmental factors among the children who ‘shared’ the overall family environments in the study by Keller et al. [46]. More than a decade ago, Klesges et al. [47] demonstrated the limited parental influences on food selection in children. In this study, 4- to 7-year-old children, who were well aware of their mother’s categories of ‘non-nutritious’ foods, nonetheless voluntarily chose such foods for lunch, unless they knew that they would be monitored by their parent [47]. In other words, the daily parental influence over the child’s eating habits during the entire early phase of the child’s life was essentially ineffectual when the child was left to his or her own devices. Parental preferences had no fundamental influence on the child’s own desired eating preference, other than they were altered by possible punitive consequences.

**Problem No. 9**

*We know virtually nothing about the developmental aspects of the energy expenditure term of the balance equation in very young children. Nor do we confidently know whether most aspects of childhood physical activity behaviors have really changed during the decades of the obesity epidemic.* Very little is known about how children develop physical activity behaviors. Essentially all the studies of childhood physical activity have been conducted in school-aged children. Nonetheless, one study of 4- to 10-year-old monozygotic and dizygotic twin pairs has suggested that genetic variability does not explain the observed familial resemblance in physical activity behaviors [48]. This resemblance, rather, is explained principally by the environmental factors shared within the family [48]. Recently, Sturm [49, 50] reviewed the secular changes in childhood physical activity behaviors that took place over the last two decades of the 20th century in America, coincident with the development of the obesity ‘epidemic’. The results were surprising. He found that children’s free time had declined substantially ‘because of increased time away from home, primarily in school, daycare, and afterschool programs’ [49]. Additionally, childhood ‘participation in organized activities (including sports) has increased’, while time for unstructured play correspondingly decreased [49]. Further, time spent watching television actually declined at the start of the obesity ‘epidemic’, but time spent in transportation increased [49]. Finally, there were not indications that increased homework has led to less available free time [49]. Overall, the changes found in children’s physical activity over the last two decades have been smaller than generally believed.
Conclusion

Despite the deceptive simplicity of the energy balance equation, its practical application in the prevention and/or treatment of childhood obesity is not a simple issue at all.

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Discussion

Dr. Lagercrantz: This was very interesting but you didn’t mention anything about the effect of breastfeeding. I would think that breastfeeding would be good for the babies. The paradox is that the prevalence of breastfeeding in France is very low and the prevalence of obesity is also low.

Dr. Bier: The data on breastfeeding with regard to obesity are very mixed and even those where the effects on the whole are put together only account for a small percent of the variance, but it is not the principal issue. One of the reasons why breastfeeding may be protective has primarily to do with the issue of infants controlling their own appetite, not with putting the extra half ounce in the bottle. The infant stops feeding, falls asleep at the breast, and finally the mother stops feeding. This may be an issue; there are people who believe it may have to do with the different flavors that babies are exposed to in breast milk, etc., but again the data are very noisy. If you look at the standard errors in some of the meta-analyses they are very large, and some total differences are relatively small. It is really hard to do those kinds of cross-cultural comparisons because there are too many other variables.

Dr. Szajewska: I have a question regarding a study published in Nature [1]. Could you comment on this study with regard to microbiota and obesity?

Dr. Bier: I think these are very intriguing observations. As we know in other context, they tell us that the gut microbiota talk to the systemic system, and that tells us that they may have effects in a way that we never understood before. I am particularly interested in this from a developmental perspective because I think it is entirely possible that we have a microbiota system that is influencing developmental genes or developmental progression in the enterocyte, for example perhaps in the intestinal lymphatic system or germ-free mice, in signals that go systemically to alter the pathways of fat oxidation in a permanent way if they are in the proper developmental window. This is one of the most interesting things that people should be pursuing from a very hard science point of view. I also think it would be extremely interesting to apply non-culture techniques to the earliest times in infancy when colonization takes place.

Dr. Strandvik: There is one problem which I would like to hear your opinion on. By advising very low fat intake, the consumption of carbohydrate beverages has increased. Could that trigger insulin which then induces the consumption of large food portions? Another thing which has been discussed is that fat consumption has not decreased but it also has not increased. What has happened in the last decades is that due to our restriction of saturated fat we advise a lot of n-6 fatty acids which are adipogenic. I wonder especially about fast foods where there are a lot of items fried with vegetable oils containing high amounts of n-6. Could that be one part of the epidemic? We also have to realize that corn is being exchanged for other seeds in the world, replacing the more original kind of feeding. What is your opinion about the hypothesis that the increase in n-6 fatty acids worldwide might contribute to the obesity epidemic [2]?

Dr. Bier: There have been a very significant number of highly controlled clinical research center studies which have unequivocally shown that a calorie is calorie, either in weight maintenance or weight reduction. If you look at the curves or the numbers, when the macronutrient content of the diet was surreptitiously changed, it didn’t make any difference, it was an energy issue. Now when it comes to whether or not there are certain things that people are consuming more of many people argue that, for example, soft drinks are contributing to extra calories, and they are. But remember when diet records and surveys are done, how precise and accurate can they be? When it comes to these kinds of data, it is much easier to identify a can of soft drink in a diet survey than it is the hidden fat in a pastry or something else. So part of the reason why some of these things may drop out may have nothing to do with the fact that it is a soft drink, it
may have to do with the fact that the variance is less in that particular measurement. When we talk about things like soft drinks, they are not energy-dense compared to fat. Whether it is an excess of calories by carbohydrates or an excess of calories by fat, people are eating too much. I am not familiar with the other parts of the world, but for years national survey data have been collected in the United States, and they tell us that people are doubling the prevalence of obesity without eating anymore. Now if you believe this, we are at a standstill somewhere; it just doesn't happen.

**Dr. Strandvik:** We investigated healthy 4-year-olds and the results showed that the children who ate more fat were slimmer than those who ate less fat and also had a higher carbohydrate intake. But one point which was very interesting was that the overweight and obese also had less n-3 fatty acids in the diet [3]. So what is happening is the ratio between n-6 and n-3 fatty acids has changed a lot. Although I agree with you that these big portions contribute to obesity, the kind of fat has a different impact on gene expression and this factor might be of importance in this change in quality of fat.

**Dr. Bier:** Very extensive studies have been done in rodents, and others have tried to reproduce them in human infants but were unable to show any difference in energy expenditure or growth depending on those fats. When I look at the sum total of the metabolic data on obesity over several decades, where people have tried every possible macronutrient permutation, my impression is that a calorie is a calorie, and it certainly doesn't make such a dramatic difference to account for the nature of the vast difference on obesity that we have. That is my belief.

**Dr. Walker:** What generally happens in the United States when we see an overweight child is that the parents are both also overweight or obese. If you go to China where one sees increasing numbers of children who are overweight, their parents are not obese. How do you explain that phenomenon in a single generation?

**Dr. Bier:** Because they are giving their children the food they would have eaten had they had the opportunity. People become obese by sitting around and doing nothing. It is actually really hard to become that obese unless you are overeating. So more calories are going in than the energy is being expended.

**Dr. Walker:** That is my point. It is not a pure genetic phenomenon; it appears also to be an environmental phenomenon.

**Dr. Bier:** The distribution of the curve is set by the genes. I don't know if any of you have ever participated or tried to do overfeeding experiments. Ethan Sims in the United States started these in the 1960s in prisoners who were fed Swanson TV dinners. He discovered, as have various people since then, that when you try to overfeed people there are some whose weight changes 1 g for every calorie, 4 g for 4 calories they receive, and other people who burn this off because suddenly their metabolic rate changes dramatically. This is a wide variance and it is set by the genes. This is also going to be true in some Chinese children who are going to get fatter and others who are going to deal with it well. It moves the distribution of the curve, and where they are is set by the genes.

**Dr. Gluckman:** The difficulty is the use of the word heritability, which is not necessarily the same thing as genes. There are many aspects of heritability other than genes: there is the environmental component; there is the epigenetic component which can be either direct or indirect through re-creation of the developmental niche which triggers the change in the next generation. We have to be very careful just to be certain of what we are talking about. For instance, looking at the transgenerational correlations in birth size and birth weight, the work of the Aberdeen study [4] highlights the other ways in which this can occur rather than necessarily just being a genetic explanation for heritability. But putting that aside, the conclusions are still the same that in fact these things occur very early on. Certainly in our experiments in animals and, in fact, the clinical data show that many children are getting visceral obesity.
from birth. Other studies very clearly show that hardwiring and changes in appetite regulation are there before any other phenotypic changes; so that is happening very early in life. The basic point we are making is that if the cycle is going to be broken, then yes we have got to deal with the macroenvironment because ultimately, whatever your hardwired physiology is, it is the environment you live in which either leads to you manifesting disease or not. If we are going to tackle this we have to think about the early developmental origins for how we can actually intervene if it is not genetic, otherwise the only way to intervene is to try to reprogram or re-hardwire, or we have to think of the thing we can’t do which is persuade people to eat less and exercise more. Just on the side, there is extensive animal or comparative biology literature on organisms in the gastrointestinal tract causing epigenetic changes in physiology. What is your opinion on this interest in the macronutrient balance in terms of appetite regulation, namely that the change in the protein to carbohydrate lipid ratios may play a role in determining when satiety occurs?

Dr. Bier: The last one first, again the literature is very noisy on this but I think it is plausible, just like the change in the different kinds of fats. One can show that these different mechanisms exist but trying to show what fraction they contribute to human obesity is very difficult because these things contribute a small fraction of the variance and showing it in some systematic way requires huge numbers of people, it is just very hard to do. The heritability, gene factor, I completely agree with you that there are some parts of the environment that are extremely difficult to tease out from the genes and some studies suffer from that more than others. In most cases the heritability estimates of factors relative to body weight are so high that even if they go down 10% on this basis, they still account for the majority of the distribution. It is an important point and I agree entirely that this heritable environmental factor is perhaps setting the development of programming that permanently keeps the memory.

Dr. Netrebenko: Several studies have been done on infant nutrition, some in United States by Stettler et al. [5] and others, showing that high weight gain during the first 4 or 6 months results in obesity at 7 years. I wonder what kind of nutrient could cause obesity if the children only receive it during the first 4 months of life?

Dr. Bier: This is again highly controversial. I have a very fundamental feeling about early weight gain as we have been unable to change the trajectory of weight gain in any group in a systematic way. The earlier a person starts to get fat, the fatter they will be at the end, regardless of what happens in between, because nothing that physicians or parents or anybody has done has been able to change that trajectory. If for example a child at that age has the right genes for catch-up growth plus has been overfed, then he starts getting fatter earlier, and that by the way has some other effect on hardwiring appetite and satiety centers; they end up being fat later. We just don’t know, but what is clear is that this is something that starts early. Early development actually starts with the mother and if we are going to be effective we have to be a generation ahead, and in fact for girls, we have to be two generations ahead to really change this.

Dr. Koletzko: This issue of early weight gain as a predictor of later overweight and obesity has been looked at in a large number of studies, far more than 20 now and 3 meta-analyses. All have described that rapid weight gain in early life, not only in the first 4 months but in infancy and early childhood, is associated with a 2- to 3-fold higher risk of overweight in school age children and beyond. This somehow matches the observation that in populations of breastfed infants there is a slightly but significantly lower risk of later overweight and obesity. It is plausible that breastfeeding in fact might protect by the lesser weight gain in the population at the end of the first year. Your question then is, is that something that one can modify or is it all predetermined by genetics or other intrauterine or whatever factors? A randomized intervention study was performed in five countries in a European childhood and obesity project where healthy term infants of
normal birth weight were randomized to two different infant formulas and follow-on formulas with lower and higher protein, based on the hypothesis that this difference between breastfed and formula-fed infants might be due to the higher nitrogen intake with infant formula leading to higher levels of branched chain amino acids which then would be expected to have higher levels of insulin IGF-I. The total cohort consisted of about 1,000 children, of which roughly 300 were breastfed for 4 months and 700 were randomized to the two different formulas. The infants have now all reached the age of 2 years. It was found that with the lower protein intake the growth curves, the weight gain, weight for height and BMI matched that of the breastfed population or the WHO growth standard, whereas with the higher protein intake there was significantly higher weight for height and BMI from the age of 6 months onwards and the relative difference was maintained until the age of 2 years, even though the intervention was stopped at 12 months. So it appears that modification of micronutrient supply can actually influence weight gain in infancy and early childhood, even though obviously we would like to understand more about the underlying mechanism.

**Dr. Bier:** Any blinded randomized studies that give a clue to what may affect this trajectory are important. In this field there have been thousands of studies of all kinds and until the results are reproduced or confirmed, it remains a nice hypothesis. All of us are looking for anything that will help us change this trajectory, and then finding the mechanism for one and also putting it into practice are important.

**Dr. Walker:** I think from the studies that have been done to get people to stop smoking, the conclusion is that preventing them from starting to smoke is much more effective than trying to get them to stop smoking. I believe that gives more credence to approaching obesity by trying to prevent it from occurring and, as Dr. Gluckman and others have said, start very early. It is an important issue. One of the problems, at least in the United States, is the data that you just presented are virtually unknown by practicing pediatricians. They don’t really follow the babies that closely and they are not aware of how important weight gain is initially in the long-term effect on overweight. What we have to do is translate observations and make recommendations to those who actually see overweight children who are continuing to gain excessively.

**Dr. Bier:** The problems that we have in trying to set the child’s weight gain trajectory are firstly that we are not very good at how to do this, and secondly we have no idea what the down side risks might be. It is a research field and the kind of studies that Dr. Koletzko talked about are necessary to understand even what the limits are for any individual child.

**References**