Growth in the First Two Years of Life

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Abstract

Compared to other periods of life, infancy is a period of rapid growth, but the relative relationships among rates of linear growth, weight accretion and brain growth vary greatly during the first years of life. Additionally, while the energy requirements for body tissue deposition as a fraction of daily energy needs decrease dramatically during infancy, brain energy demands, measured as the cerebral rate of glucose utilization, increase markedly during the same period. There is now substantial evidence that postnatal growth in infancy is associated with various consequences detrimental to health in adult life, particularly hypertension, cardiovascular disease, obesity and type 2 diabetes, but the relationships vary depending on whether one takes growth to mean statural growth or ponderal growth, as well as on the specific period of infant growth. Recently, several mechanisms have surfaced that might account for the relationships observed. These include epigenetic effects on gene expression, alterations in neuronal signaling because of inappropriate dendritic pruning, and gut microbiota effects on fat storage.

Introduction

The Oxford English Dictionary defines growth as ‘the action, process or manner of growing; both in material and immaterial senses’ including ‘size or stature attained by growing’. The Cambridge Advanced Learner’s Dictionary defines growth as an ‘increase in size or amount’. The MSN Encarta Dictionary calls the growth process ‘the process of becoming larger and more mature through natural development’, while a textbook of pediatric endocrinology says that ‘growth can be defined as an increase in size by accretion of tissue’ [1]. While generally describing the same processes, differences in the precise meaning of growth to individual scientists become important for interpreting
the reported information on pathophysiology, control, and nutritional influences on normal and abnormal growth. Thus, to a pediatric endocrinologist, growth almost invariably means statural growth, an increase in length or height. To a nutritionist, on the other hand, growth often means ponderal growth, an increase in body mass. These distinctions are important because, even though length and mass increase concomitantly, some regulatory elements are common to both and others are not. Likewise, it is not unexpected, then, that some environmental influences might alter both, while others might influence weight gain, but not stature, or vice versa.

**Growth during Fetal Life and Infancy**

Fetal growth is under different controls than postnatal growth. In utero, fetal growth is influenced by factors extrinsic to the fetus, including placental function and maternal anatomical, blood flow and nutritional considerations. Intrinsically, fetal growth is orchestrated by various major gene families, like the homeobox and growth factor classes, and limited by nutrition supplied via the placenta [1]. Although the prenatal regulation of insulin-like growth factor-1 (IGF-1) is not entirely understood, inadequate postnatal nutrition impairs IGF-1 gene expression. Thus, the effects of fetal malnutrition on growth may be mediated, at least in part, by inadequate IGF-1 generation. Infants malnourished in the womb and infants who completely lack IGF-1 activity, either as a result of a defective growth hormone receptor or a mutation in the IGF-1 gene [2, 3], are both born small, as are the corresponding gene knockout animal models [1]. Fetal nutritional insufficiency during the first two trimesters tends to affect birthweight and length proportionately, but inadequate fetal nutrition during the last trimester impairs weight gain more than a decrement in length. There is little doubt that fetal growth is highly dependent on the environment in utero, including the effects of placental blood flow [4], and prevailing data suggest that intrauterine environment and fetal nutrition are the principal determinants of birth size. Nevertheless, despite dramatic improvements in maternal health and nutrition over the last century, there has been little increase in birthweight in societies keeping reliable records [5] and balanced maternal protein-energy supplementation during pregnancy results in only a very modest increase of 21–75 g in infant birthweight [6]. Although the fact that heavy mothers produce larger babies is well appreciated [4], the determinants of neonatal body composition are poorly understood. Recently, however, Harvey et al. [7] showed that maternal size, parity, and fat stores contributed independently to neonatal body composition, and Andreasyan et al. [8] demonstrated that a higher maternal protein intake during late pregnancy led to a lower infant ponderal index at birth.

There is only a weak correlation ($r = 0.3$) between birth size and adult size. However, by 3 years of age, the correlation between and length and adult
height reaches 0.8 [1]. Thus, genetic factors are the predominant influence on linear growth during the first 3 years of life. However, even though length velocity during the first 3 years of postnatal life is faster than that of any period other than fetal life, infants with ‘tall genes’ who are born short grow more rapidly during the first 3 years of life, and infants with ‘short genes’ who are born long grow more slowly during the first 3 years. Historically, the former circumstance is often interpreted to be the result of optimal nutrition and/or parental care while the latter circumstance is felt to reflect nutritional inadequacy and/or the consequence of disease.

Although a small minority of single gene defects affect growth or body-weight [9, 10], both weight and linear growth are primarily polygenic traits [10–13], and genetics are the major determinants of both adult weight and height. Silventoinen [11] has estimated that only about 20% of the variation in height is due to environmental factors, predominantly nutrition and disease. Similarly, genes account for the major fraction of variance in bodyweight [14]. Only about 2% of monozygotic twins are discordant for weight and, although the heavier adult twin weighed slightly more at birth, bodyweight discordance was only seen after puberty [15].

It is equally important to appreciate that the relative increments in length and weight during the first 2 years of life are dramatically different. Thus, from birth to 24 months of age, body length increases about 75% to a value approximately 50% of final mature height while weight increases by more than 2.5-fold, but to a mass only about 20% that of adult bodyweight [1, 16, 17] (fig. 1). Remarkably, during the same interval, brain size increases to more than 80% of adult brain size and, by the age of six, its size is 95% that of the adult [1, 18] (fig. 1). The endocrine control of body compositional changes during infancy and childhood has been extensively studied [19] and energy requirements for growth [20, 21] and cerebral metabolism [22] have now been measured. Surprisingly, despite the fact that growth is especially rapid through the first 3 years of life, the energy cost of growth as tissue deposition amounts to 40% of energy expenditure at 1 month of age, but declines to about 3% at 1 year of age [20] and remains at this low level until the onset of pubertal growth [21]. On the other hand, brain glucose consumption increases rapidly during the first few months of life, continuing to rise to about 4 years of age, when cerebral glucose consumption rates are more than twice those of the adult [22]. Further, the cerebral metabolic rate of glucose consumption remains well above the adult rate until late adolescence [22].

**Relevance**

Until recently, despite an established interest in the effects of prenatal growth on adult disease, interest in postnatal linear growth and weight gain was primarily related to diagnosing and rectifying the causes of failure to
thrive, including malnutrition, infection, and assorted other pathological conditions or genetic disorders. Concern about rapid growth was virtually non-existent. This situation changed with published data that raised the possibility that rapid postnatal growth came with a ‘cost’, namely increased risk of chronic diseases in adult life [23–29]. In this context, rapid growth refers to increased weight gain, since there is an inverse association between height and the risk of developing coronary heart disease [30]. More specifically, in reference to coronary heart disease and diabetes, the postnatal trajectory of increased weight gain does not take place until a period of slow weight gain for the first year or two of life [31] or is the consequence of an earlier than expected second rise in the childhood body mass index curve (adiposity rebound), before the ages of 5–7 years [26]. While this model has extensive support from observational studies, it is not entirely clear whether the detrimental adult outcomes (namely obesity and its comorbidities) are related to a

Fig. 1. Relative relationships among linear growth, growth in bodyweight and brain growth during infancy, childhood and adolescence. From Clayton and Gill [1], with permission.
simple mass accretion times time function. In other words, since we have had very little success in achieving and/or maintaining long-term weight loss, do the associations merely reflect the fact that individuals who start to gain excess weight at an earlier age are fatter at any given later age and more likely to suffer the consequences? An alternative model, where the critical period of rapid weight gain is the neonatal period [23, 24, 32] also has experimental support although a recent study with a contemporary cohort of infants found no relationship between weight gain in the first 6 weeks of life and height, weight, body fat or insulin resistance at 5–8 years of age [32].

**Research for Resolution**

Compelling questions arise from the observations reported above. First, how, precisely, do cells or organs ‘remember’ their environment during infancy, what they ate and how fast they grew? Secondly, what cells or organs are responsible for the integration of the information stored? Third, what does this have to do with nutrition during the first few years of life? Some plausible answers to the mechanism of memory are shown in table 1. Expected mechanisms for which there is direct evidence include genomic imprinting and CNS synaptic pruning, while a fully unexpected explanation involves the consequence of the stability of the gut microbiome.

What is now very clear is the fact that cellular environmental ‘memory’ can be held in the form of permanent marking of DNA via methylation (genomic imprinting), resulting in gene silencing. This process, in which gene expression is affected without a change in DNA structure is called epigenetics. Further, since the dietary nutrients methionine, folate, vitamin B\textsubscript{12}, choline and betaine are responsible for the cellular ‘methylation milieu’, recent evidence has shown that postnatal ‘methylation’ diets fed during the post-weaning period can permanently alter the expression of the IGF-2 gene in adult animals [33]. The full extent of this phenomenon, the specific nutritional boundaries, and the proof-of-principle experiments in human infant early nutrition have yet to be described.

Through hypothalamic regulation, the brain is the regulatory center of both linear growth and bodyweight regulation. MRI and PET studies demonstrate the very high degree of metabolic activity in the human infant brain during

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early infancy [18, 22] and the proof-of-principle experiments of nature that link gene methylation to altered CNS regulatory experiments have been described. Thus, Rett syndrome (and possibly other autism spectrum disorders), a severe developmental regression syndrome associated with impaired growth in girls, is the consequence of abnormal gene methylation in the CNS that affects neuronal transcription and synaptic activity by interfering with dendritic expansion and pruning [34–36]. Similarly, in addition to well-described fetal animal programming effects on appetite and obesity [37–40], there is now clear demonstration that hypothalamic feeding circuits are programmed during critical early developmental periods in rodents by leptin effects on the development of neuronal connections from the arcuate nucleus [40, 41], and that leptin treatment during the appropriate critical period can reverse developmental programming effects [41, 42]. Further, others have shown that variations in maternal care during infant rodent suckling can result in epigenetic alterations in hippocampal gene expression in adult animals and, perhaps more importantly, that these epigenetic markings are reversible later in life by provision of the methyl donor, methionine [43, 44].

Finally, rather surprising new developments raise the possibility that bacterial colonization of the neonatal gut may play an important role in infant weight gain. Recently it has been demonstrated that (a) microbial colonization of the gut increases calorie extraction from plant polysaccharides ingested in the diet, (b) the specific population of gut flora is unique to an individual and is remarkably stable within an individual over time, (c) the relative abundance of the two principal bacterial divisions, the Bacteroidetes and Firmicutes, regulates fat storage in the host animal by two independent mechanisms, alteration of fasting-induced adipose factor and phosphorylation of AMP-activated protein kinase, (d) that the relative population of gut Bacteroidetes in obese adults is reduced compared to lean individuals, and (e) that obese individuals subjected to dietary weight loss regimens increase the gut Bacteroidetes to Firmicutes ratio toward the value found in lean subjects [45–48]. Clearly, these observations should be pursued during the initial period of neonatal gut colonization and as a function of the types of milk fed to infants, the time of weaning and the nature of weaning foods in order determine if gut bacteria play any role in the differences in weight gain found in breastfed and formula-fed infants or in defining optimal weaning foods and regimens to help prevent childhood obesity.

References


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**Discussion**

*Dr. Barker:* Can I respond to your point about the adiposity rebound. In the Finnish data your point is correct in that the rates of increase in BMI after the adiposity rebound are the same whatever the age at the adiposity rebound, so it is true that you are fatter at 10 if you have an early adiposity rebound because you simply started earlier. It is like elephants being bigger because they grow for longer not because they grow particularly fast. The magic is why do you start early? Why does a thin 1-year-old get triggered into an early adiposity rebound? That is the magic and we know nothing about it.

*Dr. Bier:* I agree with that completely. I think it relates to more fuel, and the genetic background. We absolutely don’t know why that happens, and I think that is a very important thing that we just don’t understand.

*Dr. Walker:* We have all seen twins who were born strikingly different in size and weight and which seems to persist through life. You said that birthweight and twin genetic effects seem to be dominantly controlled. Is there something going on in utero that has affected the long-term difference in the size and height of these twins?
Dr. Bier: First a lot of twins that are born discordant are dizygotic, not monozygotic twins, so it is a different category. There are clear examples in which a twin has been affected in some way, presumably by something in the intrauterine environment, that is different than the other twin, and they maintain some of those differences. I am not sure that this is different from when, for example, twins are reared within supposedly the same extrauterine environment; we think it is the same environment but it is different. We talk a lot about the fact that the family and the environment need to be the same, but there is a significant body of data showing that the unshared environment of that individual child has a direct effect, and I think it may be the same in utero, I just don't know.

Dr. Walker: Gordon et al. did studies looking at the nature of the bacterial flora in individuals who are overweight and obese and those who are slim, which show that they might represent different microflora. There may not be just an adverse effect, an increasing weight, but there may be microflora that control a decrease or maintenance of normal weight.

Dr. Bier: The flora distribution is related not only to the weight of Ob/Ob mice compared to lean mice but obese adults compared to lean adults. The gut flora change with restricted carbohydrate or fat diets. What has also been demonstrated using molecular methods, which have not really been applied much to newborn colonization to any great degree, is that the colonization is actually remarkably stable within an individual until the diet changes or their weight is reduced, and then it changes. This has clear implications for types of formula feeding, the introduction of solid foods, and all those things that we are talking about in early infancy.

Dr. Ogra: Do you have any opinion as to what comes first, the altered microflora or the metabolic changes? Is it possible that acquisition of the altered flora is the result of the metabolic changes that have taken place in the host?

Dr. Bier: Actually Gordon et al. have now published a series of studies in PNAS and Science, and I think these are things that people who are interested should look at because they have done all the controls. They have introduced the flora to germ-free animals and shown the changes as a result of that; they have taken animals which were genetic knockouts of the fat-induced adipocyte factor and showed that they don't respond to the change in bacteria. They are really elegant experiments.

Dr. Ogra: The second question relates to the memory these cells maintain for genetic information. Are there any data on programmed cell death being altered or mediated through changes in nutrition or by triglycerides, for example?

Dr. Bier: There are certainly some data on some change in programmed cell death and its consequences; whether they are nutritional or not, I am not entirely sure about that.

Dr. K. Bergmann: You said that you don't know anything about what could influence the adiposity rebound, that it just occurs. In our study on the effect of breast feeding on the emergence of overweight and obesity, the main finding was that breastfeeding postponed the adiposity rebound. Perhaps something could be done about it.

Dr. Bier: My simplistic view of the world is that you eat or you don't eat, and this could be entirely due to a difference in energy intake. We have virtually no way of telling the energy intake of free-living human beings. We can tell energy expenditure but all the data on intake are highly variable and flawed. Again I would say this could merely be the result of a small difference in energy intake in infants who are being formula-fed and getting the extra ounce in the bottle versus the breast-fed infant who stops feeding. No one has talked about this but I think one of the major benefits of breastfeeding is that it allows the infant to turn off the feeding.

Dr. K. Bergmann: In our observation there weren't any differences until the start of the rebound and that was much later than the weaning period. So it should have programmed something in the infants to perhaps not take as much milk.
Dr. Giovannini: What is your opinion on how long the programming effect of nutrition persists in later infancy? When would you suggest starting a diet controlled for lipid intake?

Dr. Bier: As far as the length of programming is concerned, I think that there are mouse data but there are no corresponding human critical periods, and we need to find a way to get those. I think one of the lessons of history in pediatrics and developmental biology has been that you are developing throughout your life. We have now very clearly seen neurologic changes in development in teenagers and things that we never thought would exist by the science we knew before. My guess is there are developmental windows all along. The ones that deal with feeding I am concerned about how these are changing permanent appetite/satiety mechanisms and whether they are related to special things in breast milk, whether they are related to the amount of food you are getting, whether there are feedback signals from the changes in adipose amount and distribution that you get with different kinds of feeding. We just need to understand that. Fat is 50% of the energy expenditure from the start, in the breast milk or formula feeding. So the type of fat may become very important. There are a significant number of studies showing that after the infant is weaned the actual fat content of the diet, as a fraction of calories, drops for a period of between 6 months and maybe 1.5 or 2 years, and that is the introduction of the low energy dense non-fat foods. We don’t know whether this is good or bad.

Dr. K. Bergmann: You said there was no correlation between birth length and adult height. But the interesting thing is that there is channeling of birth height to adult size like McCance and Widdowson showed in their very early studies on channeling in the Bundy population in Great Britain. Those who were shorter at birth remained shorter until adult life.

Dr. Bier: The channeling is stronger and stronger the older you get, and at the beginning there are certainly changes in centiles in some fractions of the population.

Dr. Cameron: The change in correlation is around at 0.2 at birth to about 0.7 or so by 4–5 years of age. It was always said years ago that that was because the infant was recovering from the constraints upon growth because of the size of the mother. But over the first 2 years it is maintained that there is a process of growth assortment occurring which we see in the growth charts of the child changing in terms of their growth canal. I am not sure what you mean by channeling from birth to adulthood. Certainly channeling or canalization from about 3 years of age upwards but certainly not between birth and upwards.