

Chapter 2

The Concept of Phenotypic Induction ('Programming') and Implications for Growth

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Abstract Growth patterns in early life have been strongly associated with the risk of diseases such as stroke, hypertension, type 2 diabetes, obesity and cardiovascular disease in adulthood. This has focused attention on the long-term consequences of developmental plasticity during early life periods of sensitivity. Epidemiological studies have consistently associated both (a) low birth weight and (b) increased childhood weight gain, obesity, rich diet and physical inactivity with risk of degenerative metabolic diseases. This chapter presents a model focusing on the development of 'metabolic capacity' during the growth periods of fetal life and early infancy and the development of 'metabolic load' during subsequent growth periods. Metabolic capacity emerges during early 'critical windows' and refers to traits such as nephron number, pancreatic B-cell mass and other components of organ structure and function. Metabolic load emerges primarily from early childhood onwards and is characterised by traits such as tissue masses, dietary glycaemic load and metabolic inflexibility. Using this model, a high ratio of metabolic load to metabolic capacity increases the risk of degenerative diseases by inducing alterations in blood pressure, insulin metabolism and lipid metabolism. Moderate normalisation of metabolic load is possible with few ill effects, but high metabolic load (e.g. from obesity) exacerbates the deleterious consequences and induces disease. An increased metabolic load during early infancy also appears to have long-term deleterious effects. However, the long-term consequences of infant growth rate appear to vary between populations, and public health policies for developing countries should not be based on studies conducted in industrialised populations. This model of the phenotypic induction of metabolism highlights the notion that adult disease risk is the product of 'disordered growth' between different growth periods. No single period of growth is critical in the induction of disease risk; rather, a number of scenarios are possible, in each of which metabolic load interacts with metabolic capacity to determine disease risk. The key implications for paediatricians are that growth rates have long-term as well as short-term health consequences, and the optimal growth pattern is likely to reflect a trade-off between costs and benefits in different periods of the life course. Public health policies must also take into account the fact that metabolic profile emerges throughout the life cycle and reflects trans-generational influences.

Abbreviation

CVD Cardiovascular disease

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2.1 Introduction

Until the 1980s, the degenerative diseases most responsible for morbidity and mortality in industrialised populations were generally attributed to the combination of genetic risk factors and adult lifestyle. Indeed they were often termed ‘lifestyle diseases’, considered to derive from poor diets, inadequate physical activity levels and unhealthy behaviours such as smoking or excessive alcohol consumption.

This perspective changed profoundly following pioneering work by Barker and colleagues, studying the epidemiology of degenerative diseases in those for whom early life experience could be reconstructed (Barker, 1998). Interest in the possible early origins of adult diseases initially arose following observations that adult mortality was often correlated with infant mortality, suggesting a possible long-term influence of conditions during early life. When the first longitudinal analyses on this issue were conducted, the results were provocative. The earliest work consistently showed that low birth weight was a strong predictor of diseases such as stroke, hypertension, type 2 diabetes and ischaemic heart disease (Barker, 1998). These results would subsequently be replicated in numerous cohorts and settings. For example, whilst initial work tended to use data from other industrialised populations, cohorts in India and Brazil also replicated the same findings. Subsequently, postnatal growth also became implicated in the risk of the same diseases.

At the end of the first decade of the 21st century, the ‘developmental origins of adult health and disease’ (DOHaD) hypothesis has become a mainstream theme within paediatric research. Central to this hypothesis is the notion that growth rates in early life are predictive of later disease risk (Forsen et al., 2000; Barker et al., 2005). This work has thus introduced a novel issue to the paediatrician in highlighting that nutritional management not only impacts on short-term outcomes but also has profound longer term consequences. Yet despite compelling evidence that early experience is critical for later health, there remain several controversies concerning which developmental periods are important, what environmental cues are relevant and whether there is a common human physiological response or whether it differs within and between populations. These questions must be addressed in order to develop coherent public health policies and appropriate guidelines for the clinical management of individuals.

2.2 The Concepts of Phenotypic Induction and Programming

Early work on the developmental origins of adult disease comprised epidemiological analyses rather than theoretical exploration, and a clear theoretical basis for this component of development is still consolidating.

In fact, independent of the epidemiological cohort studies, nutritional scientists had been investigating the process of growth in animal studies for several decades. In the 1960s, two British scientists showed that the effect of malnutrition on rats differed markedly according to the period of growth affected. Whereas malnutrition during the period of gestation or lactation permanently reduced size, malnutrition following infancy only slowed growth temporarily, such that the trajectory of growth was restored rapidly following a resumption of normal food supplies (Widdowson and McCance, 1960). This work, complemented by similar work on the development of the brain (Davison and Dobbing, 1968), indicated the possibility of ‘sensitive’ or ‘critical’ periods in development. Such critical periods apply to many aspects of development and are well known in non-human species such as the behavioural imprinting characteristic of some birds, but their sensitivity to nutrition had received little attention.

Such work suggested that whereas growth rates in early life in mammals are relatively plastic, around the time of weaning canalisation tends to occur, with growth trajectory becoming 'self-righting' following nutritional insult (Tanner, 1963; Smith et al., 1976). This work is fundamental to current work on the early origins of later disease risk, focusing in particular on what happens during early windows of plasticity and what the long-term effects are. Some of the first studies to reveal the long-term effects of early nutritional variability were conducted on baboons. Lewis and colleagues (1986, 1988) showed that infant nutrition was associated with both adiposity and cardiovascular risk in adulthood. Significantly, the enhanced fatness of adults overfed in infancy developed post-puberty.

Building on this animal work, Lucas and colleagues initiated a series of trials in humans, randomising infants in the postnatal period to different diets (Lucas et al., 1984). This work emphasised the concept of 'programming', which Lucas (1991) defined as the capacity of environmental stimuli during critical developmental periods to exert long-term or permanent effects on subsequent structure and function of the organism. The terminology of programming has subsequently entered into widespread use amongst the medical community. However, it has been criticised by the evolutionary biologist Bateson (2001), on the grounds that it incorrectly suggests that early life experience contains 'instructions' for later disease states. Many authors for example refer to the programming of obesity or hypertension; yet, these diseases are in fact complex composite traits responding to numerous exposures across different developmental periods.

Bateson (2001) proposed instead the term 'phenotypic induction', as a broader phrase appropriate for application across a wide range of biological disciplines. To some extent, the two terms can be used interchangeably; however, phenotypic induction is in my view preferable because it facilitates the incorporation of different stimuli impacting on phenotype throughout development. Whereas the programming approach places particular emphasis on those expressing ill health in later life, the broader approach regards all individuals as responding to their successive environments. The benefits of this approach may become apparent during the discussions that follow.

The concept of phenotypic induction is illustrated in Fig. 2.1. This schematic diagram shows that phenotypic variability can develop in response to environmental stimuli during early sensitive periods. In postnatal life, these plastic periods terminate, such that whatever variability is present tends to track on through adolescence into adult life. However, only some traits may be considered to be induced in this way. As will be discussed in greater detail below, other components of physiology retain plasticity and hence mediate the impact of subsequent environmental conditions.

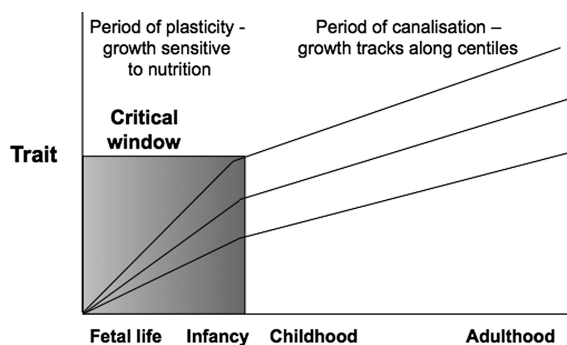


Fig. 2.1 Schematic diagram illustrating the concepts of phenotypic induction (programming) and tracking. Phenotypic induction occurs through developmental plasticity during early 'critical windows' of physiological sensitivity, when environmental factors induce variability in a range of phenotypic traits such as the size and structure of organs. As the windows of sensitivity close, these traits tend to track onwards into adulthood, such that the early environmental factors exert long-term phenotypic effects. The body accommodates these long-term effects in some traits (e.g. nephron number) by maintaining plasticity in others (e.g. blood pressure)

2.3 The Classic Study of the Dutch ‘Hunger Winter’

Perhaps the first study in humans which drew attention to the potential importance of early life experience for later health was a follow-up of adults exposed to malnutrition in utero during the Second World War. During the ‘Dutch hunger winter’, a portion of the Dutch population was suddenly exposed to a drastic reduction in food rations. Some months later, the famine ended and adequate food supplies were rapidly restored (Ravelli et al., 1976). Detailed studies have illustrated the consequences of this experience for those gestated during the famine, both in terms of birth weight and in terms of adult phenotype. Of particular scientific interest, it has been possible to differentiate those who were exposed to maternal famine during specific trimesters of pregnancy. A landmark publication showed that compared with young adult men who had not experienced maternal famine in utero, those who had been exposed had higher adult BMI if they had experienced maternal famine in the first trimester of pregnancy, but lower BMI if they had experienced maternal famine in the third trimester (Ravelli et al., 1976). These data were collectively suggested to indicate the induction of either adipocyte number or appetite regulation, depending on when the malnutrition exposure occurred. Longer term follow-up studies reported similar associations between early pregnancy exposure to maternal famine and markers of obesity in middle-aged women, but did not reproduce the earlier findings in middle-aged men.

The notion that fetal nutrition might be the critical underlying mechanism in such associations appeared to be supported by birth weight data. Compared to those not experiencing maternal famine, those exposed to famine in the third trimester had significantly reduced birth weight. However, those exposed to famine in the first trimester did not have reduced birth weight (Stein et al., 2004).

Paradoxically, these findings were not replicated in a very similar cohort, who had been exposed to famine during the siege of Leningrad, also during the Second World War. In this population, no association was observed between maternal malnutrition in utero and subsequent phenotype, despite an even bigger deficit in birth weight (Stanner and Yudkin, 2001). An important difference between these populations is that whereas the Dutch population experienced a sudden relief from famine, the Leningrad population continued to experience malnutrition for several years. As discussed in greater detail below, this indicates that the association between fetal nutrition and adult health profile is mediated by patterns of postnatal growth.

2.4 The Fetal Versus Postnatal Growth Controversy

Whilst the Dutch hunger winter study provided the first significant data set on the long-term consequences of early nutrition, the issue had already attracted attention elsewhere. Epidemiologists observed that adult mortality tended to be positively associated with infant mortality, even though the causes of death differed across the lifespan. This indicated that tough conditions early in life might have long-term effects on survivability. From the late 1980s, epidemiologists began to study data sets collected during the early to mid-20th century, in order to explore in more detail associations between early experience and subsequent health outcomes. The first results to be published came from the Hertfordshire cohort, born in the 1930s in the UK and followed up 50 years later (Barker, 1998).

Perhaps the key finding to emerge from such early analyses was the strong inverse association between birth weight and subsequent disease risk (Barker, 1998; Barker et al., 2002). Although attention focused in particular on the enhanced disease risk of those born small, studies repeatedly

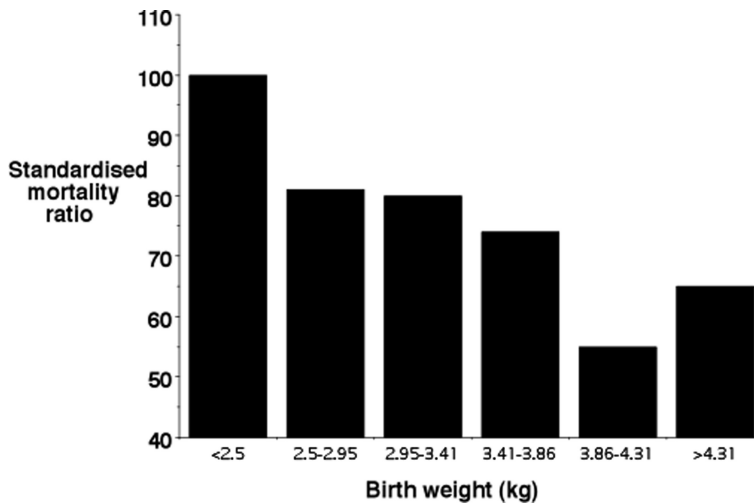


Fig. 2.2 Standardised mortality ratios according to birth weight in the Hertfordshire cohort. The figure shows an inverse association, indicating that taking into account current weight, mortality increases with decreasing weight across the range of birth weight (Barker, 1998)

demonstrated a negative dose–response association between birth weight and subsequent risk across the range of birth weight (Barker, 1998; Barker et al., 2002). Figure 2.2 shows for example the association between birth weight and risk of ischaemic heart disease in the Hertfordshire cohort study. Initial interpretation of these findings focused on the apparent importance of fetal nutrition for adult health, and though this issue has subsequently become a topic of fierce debate, the findings were sufficiently robust to challenge the prevailing view that differences in cardiovascular risk were primarily attributable to genetic factors or adult lifestyle. Hales and Barker (1992) proposed the ‘thrifty phenotype hypothesis’, arguing that low birth weight should be considered a ‘survival phenotype’ induced by poor fetal nutrition. The survival phenotype would be beneficial in early life, but would predispose to metabolic costs in later life, especially if challenged by a high-quality diet. Their model attributed these long-term effects to the fact that the structure of most vital organs develops in utero or during infancy, such that it is not possible for the effects of early malnutrition to be fully compensated for during later periods of growth.

As the inverse association between birth weight and cardiovascular risk became replicated across diverse cohorts, both in industrialised populations and in developing countries, it came to attention that the link emerged most strongly, or in some cases only, following statistical adjustment for current weight (Lucas et al., 1999). In other words, holding current adult weight constant, disease risk was found to be greatest in those born small, though once again the effect was discernible across the range of birth weight.

Lucas and colleagues (1999) argued that a more appropriate interpretation of such statistical models was that variability in disease risk could be attributed to *change* in size between birth and adulthood. This approach focuses attention on postnatal rather than fetal growth, in other words the trajectory of weight gain during infancy and childhood. Subsequently, Singhal and Lucas (2004) argued that variability in disease risk could be attributed entirely to postnatal growth patterns. Their ‘growth acceleration hypothesis’ stemmed from their work on randomised trials of infant diets, which showed long-term effects of early growth variability independent of size at birth.

To some extent, these perspectives do not actually differ. A large number of studies have now converged on the hypothesis that disease risk is greatest in those born small who subsequently become

Table 2.1 Studies demonstrating high risk of the metabolic syndrome in those born small who become large

Population	Disease trait or marker	Author
Filipino adolescents	Blood pressure	Adair and Cole (2003)
Indian children	CVD risk (insulin resistance, blood pressure, glucose tolerance and plasma lipids)	Joglekar et al. (2007)
Indian adolescents	Glucose tolerance	Bhargava et al. (2004)
Swedish adult men	Blood pressure	Leon et al. (1996)
Finnish adults	Type 2 diabetes	Forsen et al. (2000)
Finnish adults	Coronary events	Barker et al. (2005)

large, as shown in Table 2.1. A particularly informative study was conducted by Leon and colleagues (1996), who focused on the disparity between adult height and birth weight. Those with the greatest deficit of size at birth relative to adult height were considered to have undergone poor fetal growth, and these individuals had the greatest risk of cardiovascular disease. Nevertheless, in some studies an association of low birth weight with later health outcomes is apparent without any adjustment for later size, and as discussed below, it is helpful to consider the complementary contributions of growth during different developmental periods to disease risk.

The area of greatest controversy comprises infancy, where both slow and rapid growth appear to be associated with increased disease risk in later life. In the Hertfordshire cohort, body weight at 1 year of age showed the same inverse association with adult cardiovascular risk as birth weight, indicating that both fetal life and infancy are periods when poor growth induces ill health in later life (Hales et al., 1991). Conversely, in their randomised controlled trials, Singhal and colleagues demonstrated adverse effects of rapid infant growth, as indexed by childhood proxies for cardiovascular risk such as split proinsulin, lipid metabolism or blood pressure (Singhal and Lucas, 2004).

These findings are less contradictory than might appear to be the case. One of the challenges of integrating the data is that the studies have focused on different ages, used different designs and assessed different outcomes. Close attention to these differences allows the findings to be integrated successfully within a single model of disease aetiology (Wells, 2009a).

2.5 A Physiological Model of the Development of Metabolic Phenotype

As recognised by Hales and Barker (1992), the structure of vital organs develops primarily during fetal life, the period of growth when the vast majority of the rounds of cell division occur (hyperplasia) (Bogin, 1988). Organ phenotype is therefore highly sensitive to fetal nutritional experience. Physiological traits such as nephron number, cardiac structure and pancreatic beta-cell mass are strongly (although not necessarily exclusively) associated with fetal nutritional experience. I have referred to such traits as ‘metabolic capacity’ (Wells, 2009a), which may be considered a collective term describing the capability to maintain homeostasis. Control of blood sugar levels and blood pressure is closely associated with these physiological traits, especially in relation to the pattern of postnatal growth. However, metabolic capacity does not develop exclusively during fetal life. Some such traits continue to maintain sensitivity to nutritional experience during infancy. For example, beta-cell mass continues to increase during infancy and is therefore predicted to reflect the magnitude of nutritional intake and hence track weight gain during this period.

After infancy, growth is dominated by hypertrophy, an increase in cell size rather than cell number (Bogin, 1988). As discussed above, linear growth becomes canalised after weaning (Smith et al., 1976), and the relative size of different organs tends to remain broadly constant, linked to overall

height (Weder and Schork, 1994). Thus, whereas nutrition exerts profound impacts on organ phenotype during the period of hyperplasia, this impact becomes minimal during the period of hypertrophy. Nevertheless, other traits remain more sensitive to nutrition, including in particular adiposity, and to a lesser extent lean mass as well as the rate of maturation. Thus, greater rates of weight gain can increase tissue mass without inducing matching increases in organ mass. I have therefore referred to hypertrophic growth and its causative processes as 'metabolic load', which refers to the homeostatic burden imposed by total tissue masses on metabolic capacity (Wells, 2009a). A larger muscle mass in itself increases metabolic load, whilst increased fat mass also exacerbates it (e.g. blood pressure and insulin resistance), due in part to the harmful endocrine products secreted by adipose tissue. This load may be further exacerbated by sedentary behaviour, which reduces metabolic flexibility (the ability to balance alternative fuel sources at the cellular level) and a diet high in carbohydrates, each of which challenges the ongoing regulation of blood sugar content and cellular metabolism. Thus, metabolic load refers to the sum total of tissue masses and fuel metabolism which derive from the interactions between past and current dietary and activity patterns.

Risk of the metabolic syndrome and cardiovascular disease can then be attributed to the ratio of metabolic load to metabolic capacity, as now demonstrated by numerous studies. Using this model, it is now possible to understand the apparently contradictory epidemiological evidence, which has emerged from contrasting study designs. The logic of the approach may be expressed in purely physical terms, using the analogy of the car. According to this approach, metabolic capacity is represented by the engine and metabolic load by the total weight of the vehicle. A high ratio of vehicle weight to engine size increases the risk of mechanical failure; however, this situation can arise from variability in both engine size and total car size (Fig. 2.3). Holding the size of the car constant, the risk of mechanical breakdown is increased for smaller engines. Holding the size of the engine constant, the risk of mechanical breakdown is increased for larger cars. This model translates directly into human physiology: holding metabolic load constant, the risk of disease is increased for smaller metabolic

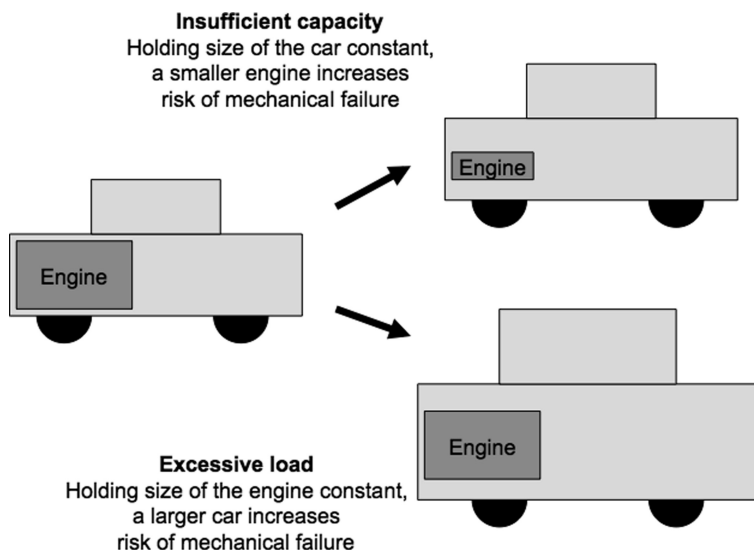


Fig. 2.3 Schematic diagram using the analogy of automobile design to illustrate the complementary contributions of engine size and total car size to the risk of breakdown. Both reduced engine size and larger car size contribute independently to the risk of mechanical failure, and their interaction is therefore derived from taking both components of design into account. This model replicates the scenario of the human body, where the engine symbolises 'metabolic capacity' and the size of the car symbolises 'metabolic load'

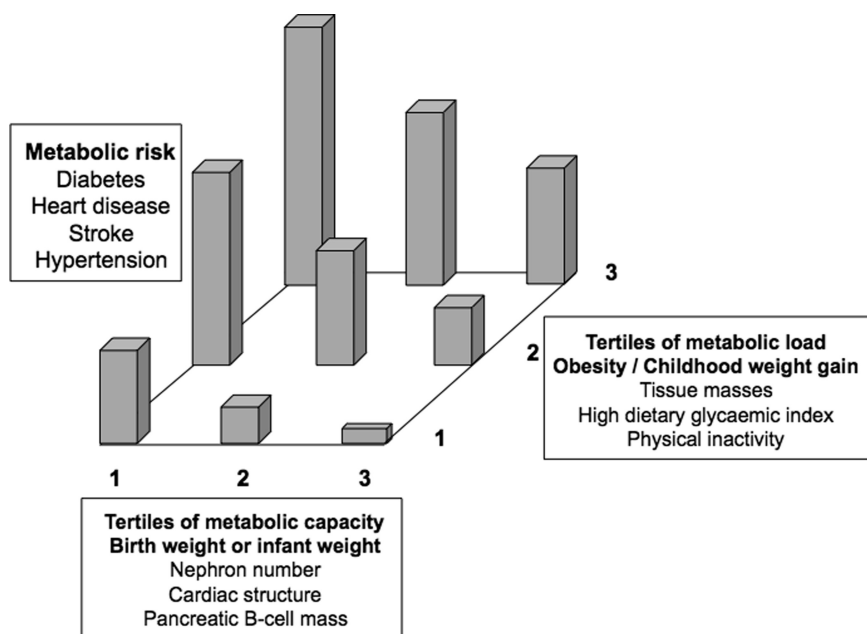


Fig. 2.4 Schematic 3-D diagram illustrating the complementary contributions of ‘metabolic capacity’ and ‘metabolic load’ to the risk of metabolic disease. For any given metabolic load, disease risk increases with decreased metabolic capacity. For any metabolic capacity, disease risk increases with increasing metabolic load. Metabolic capacity is indexed by fetal and infant size, which in turn indexes developmental traits such as nephron number and pancreatic B-cell mass. Metabolic load is indexed by the sum total of tissue masses, along with the metabolic stress induced by past and current patterns of food intake and physical activity

capacity; in turn, holding the size of metabolic capacity constant, disease risk is increased with greater metabolic load. This is illustrated in Fig. 2.4, which includes reference to various parameters of metabolic capacity and load.

This model can therefore explain why the epidemiological studies following cohorts into late adult life consistently associate, holding current weight constant, low birth weight (poor metabolic capacity) with an increased risk of cardiovascular disease, diabetes, hypertension and stroke (Barker, 1998; Barker et al., 2002; Hales et al., 1991). It can also explain why randomised trials associate rapid childhood growth rates (increased metabolic load) with indices of cardiovascular risk (Singhal and Lucas, 2004), with obesity exerting similar effects. Finally, it can explain the paradoxical findings for infancy, where both low and high rates of growth appear detrimental to later health. It is plausible that low rates of infant weight gain continue to constrain metabolic capacity, whereas high rates of infant weight gain represent an early induction of increased metabolic load (Wells, 2009a). Infancy is thus an unusual period of growth, during which both metabolic capacity and metabolic load are sensitive to nutritional experience.

Exactly how growth rates during childhood exacerbate metabolic load is becoming clear from studies of physiology. Traits such as blood pressure are sensitive to weight gain, because they play a key role in normalising the metabolic load exerted by the tissue masses on metabolic capacity. Blood pressure increases naturally during adolescence, because as body size increases whilst nephron number remains constant, a larger pressure is required to supply the tissues (Weder and Schork, 1994). Thus, whilst for a given nephron number, increased tissue mass requires greater blood pressure, so for a given tissue mass, lower nephron number will also increase blood pressure because the relative

load will be greater. The greatest blood pressures are thus found in those born small who become large (Adair and Cole, 2003).

A similar pattern of normalisation is apparent for other traits relative to metabolic phenotype. For example, insulin resistance and insulin secretion are closely related, such that in healthy individuals insulin resistance interacts with insulin secretion to maintain glycaemic control (Bergman et al., 2002). Insulin resistance may initially arise to protect tissues from the effects of hyperinsulinaemia, reflecting high dietary load. However, reduced beta-cell mass reduces the capacity to secrete sufficient insulin and hence eventually reduces tolerance of insulin resistance. Both low birth weight and high current weight therefore predict glucose intolerance and diabetes (Hales et al., 1991; Bhargava et al., 2004; Joglekar et al., 2007), but again their combination generates the strongest risk.

Whilst increased metabolic load at any time throughout postnatal life is assumed by this model to increase disease risk, the emergence of metabolic load in infancy may be especially important. Epigenetic effects are generated primarily within the window of plasticity and then continue to influence phenotype thereafter. This scenario can explain why rapid infant growth in industrialised populations tends to have long-term effects on obesity risk, as discussed below.

2.6 The Variable Impact of Catch-Up Growth

This model of disease development places particular emphasis on the contribution of catch-up growth during infancy. As is well established, infants born small tend to undergo catch-up growth during the first few months of life (Ong et al., 2000). In developing countries, this catch-up growth pattern is associated with improved survival (Victora et al., 2001), and promotion of infant weight gain has long been regarded an important public health policy. Recent studies, however, have demonstrated strong associations of rapid childhood weight gain with increased cardiovascular risk profile. Thus, one key issue is when catch-up growth should occur, in order to maximise its benefits and minimise its costs. The disease implications of catch-up growth also appear to differ markedly between populations from industrialised and developing countries, and this issue is likewise of critical importance for public health policies.

In industrialised populations, rapid infant growth has been associated with increased risk of obesity (Stettler et al., 2002) and cardiovascular risk (Ekelund et al., 2007). However, in a comprehensive analysis of data from five birth cohorts in Brazil, Guatemala, India, South Africa and the Philippines, greater infant growth was found to impact beneficially on a wide range of outcomes, without substantially increasing risk of later disease (Victora et al., 2008). In both types of population, however, rapid childhood growth is directly increased with later disease risk.

Data from India illustrate this scenario particularly well. Indian neonates tend to have substantially lower birth weight than those in the UK, with an average deficit of almost a kilogram (Yajnik et al., 2003). This reduced birth weight is associated with altered body composition, with much greater deficits in lean mass than in fat mass, whilst low birth weight Indian neonates are also hyperinsulinaemic (Yajnik et al., 2003). During infancy, greater rates of weight gain are associated primarily with increased levels of lean mass in adulthood, considered beneficial for health and metabolic phenotype (Sachdev et al., 2005). In contrast, greater rates of weight gain from childhood are associated with greater adiposity in adulthood and with poorer metabolic phenotype (Sachdev et al., 2005). A similar pattern of growth has been observed in Brazilian cohorts, where again infant growth was associated most strongly with later lean mass, but childhood growth with later fat mass (Victora et al., 2008).

These findings thus suggest that catch-up growth in developing countries, where low birth weight remains common, may be beneficial if it occurs within the first 2 years of life (although the exact duration of the beneficial window and the optimal magnitude of catch-up should be established with more confidence). The key question is therefore how to target growth at the specific developmental periods where it is most beneficial. A solution to this dilemma may be emerging following improved understanding of the hormonal regulation of early growth.

Leptin acts as a signal of energy stores to the brain. During pregnancy and lactation, maternal leptin passes to the offspring and hence ‘overestimates’ the offspring’s own energy reserves, thus encouraging it to deposit lean rather than fat (Wells, 2009b). Administration of leptin to small infants may therefore promote healthier weight gain during infancy, with long-term beneficial effects.

Likewise, the rapid infant growth of small-for-gestational age babies appears to be driven by high levels of insulin secretion (Soto et al., 2003), which favours increased rates of linear growth during infancy. Around the time of 2 years, if rapid weight gain continues, insulin resistance develops along with an increased rate of central fat deposition (Ibanez et al., 2006). This central fat then plays a key role in the emergence of other detrimental traits such as greater blood pressure, adverse lipoprotein profile and reduced glycaemic control. According to this perspective, the early childhood diet is a key mediating factor linking child growth with adverse metabolic profile and is the ideal target for intervention. The obesogenic niche effectively acts as a magnifying lens, providing a high level of energy intake during a period of growth when, prior to the invention of modern energy-dense foods, low energy intake would have been the norm.

2.7 An Evolutionary Perspective

Up to now, this chapter has considered phenotypic induction as a process occurring in each generation. Growth patterns induce later phenotype and hence health, with low birth weight associated with poorer phenotype and health in adult life. Whilst this perspective is valuable for identifying the key period of sensitivity, and hence the optimum time points for specific interventions, it artificially isolates within a single generation a process which actually occurs across generations. Phenotypic plasticity evolved in order to protect the genome from selective pressures and allow development to adapt to more recent or prevailing ecological conditions.

The patterns of fetal growth that initiate the process of phenotypic induction in each generation are largely the product of the nutritional experience of the prior generation. Nutritionists have long been aware of secular trends in growth that occur across generations, most notably upwards in recent decades in industrialised populations, but in other global regions downwards in response to deteriorating ecological conditions (Wells, 2010). Phenotypic plasticity allows each generation to ‘guide’ the development of the next one. Much of this guiding occurs during pregnancy, when uterine phenotype impacts strongly on the development of the fetus. Greater flexibility characterises infancy, such that the small baby may be able to catch-up following fetal growth restraint if adequate nutrition is available.

This trans-generational plasticity allows human populations to adapt to changing levels of nutritional supply. Body size decreases when energy availability falls and increases when energy availability improves. However, when this trans-generational process is compressed into within-generational time spans, the metabolic costs are exacerbated (Wells, 2010). Fetal life and infancy are the primary periods during which nutritional supply can induce a larger body size. From early childhood onwards, because height is canalised, increased nutritional supply primarily affects weight rather than height and exacerbates metabolic load. It is the emergence of the obesogenic niche with

Table 2.2 Key points

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1. Compelling evidence now links early and childhood growth rates with later disease risk
 2. The paediatrician must now consider that growth has both benefits and costs, and that these benefits and costs may be realised in different periods of the life course. This has implications for nutritional interventions in both infancy and childhood
 3. The impacts of infant catch-up growth appear to differ by population, and it remains uncertain what the optimum rate of infant weight gain is, how long growth should be promoted in any given population and what characteristics of populations should be taken into account when making such decisions
 4. One particularly intriguing issue comprises ethnicity, as ethnic groups appear to differ in their associations between nutritional status and disease risk
 5. Future research should establish how much of this differential disease risk can be explained by the model described here focusing on metabolic plasticity and metabolic load (which would implicate past patterns of growth in recent generations) and how much can be explained by genetic factors (which would implicate deeper ancestral experience)
 6. Public health policies need to take into account the fact that metabolic risk is the consequence of accumulating exposures across the life course
 7. There is a need for coherent policies that, at any given life-course period, complement those impacting other periods
 8. Traditionally, policies in developing countries have promoted growth throughout infancy and childhood. Recent comprehensive analyses indicate, however, that the benefits of increased growth are limited to within the first 2 years of life (Victora et al., 2008)
 9. Studies are now required to determine how to capture the benefits of this early growth whilst avoiding detrimental rapid child weight gain
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unprecedented high levels of calories and little demand for physical activity that is facilitating the exacerbation of metabolic load, particularly in those whose metabolism predisposes them to this on account of their upregulated infant growth.

In this context, ethnicity emerges as a particularly important factor. Ethnic groups are known to differ in the disease risks associated with particular levels of nutritional status. This differential disease risk may in part derive from recent ancestral variability in growth patterns. For example, the lower average birth weight and reduced metabolic capacity of south Asians may derive from poor nutrition in recent generations (Wells, 2010), rather than genetic adaptations in more distant ancestors. Testing these ideas, to understand the contribution of plasticity to ethnic variability, is critical for formulating appropriate public health policies for developing countries, as well as managing individual patients.

Growth is now a well-established determinant of later health, and several issues are critical for paediatricians (Table 2.2). Paediatricians must also be aware that the optimal pattern of growth at any age is a compromise between health costs and benefits realised at different times through the life course. Key questions meriting further attention are how to boost metabolic capacity without exacerbating metabolic load and how to limit metabolic load without constraining metabolic capacity.

2.8 Applications to Other Areas of Health and Disease

The developmental origins of adult disease hypothesis are increasingly considered integral to many areas of human health and have particular importance as discussed above for understanding the life-course emergence of disease profile and the trans-generational nature of this life-course progression. Many areas of adult health increasingly take early life factors into account, for both

non-communicable and infectious diseases. Furthermore, the implications of research in this area apply not only to public health nutrition policies and clinical paediatrics but also to policy relating to agriculture and the food industry, as well as social issues relating to the pattern of sexual maturation.

Summary Points

- There is now compelling evidence linking growth patterns in early life and childhood with the risk of metabolic disease (type 2 diabetes, hypertension, stroke and coronary heart disease) in later life.
- Holding current size constant, poor growth in fetal life and early infancy is strongly associated with increased disease risk. Holding birth size constant, increased childhood growth rates are associated with risk of the same diseases.
- A physiological model based on metabolic capacity (directly associated with early life growth) and metabolic load (directly associated with weight gain, rich diet and physical inactivity from childhood onwards) can explain these observations. A high ratio of load to capacity increases disease risk.
- The effects of growth in infancy appear to vary between industrialised and developing countries. This may relate to differences in birth weight and the magnitude and duration of infant catch-up growth. Studies from industrialised countries are not appropriate for generating public health policies for developing countries.
- The induction of phenotype occurs across as well as between generations. The most successful health policies are likely to be those that provide coherent benefits across generations and life courses. The model used here indicates that the promotion of metabolic capacity should be complemented by the reduction of metabolic load.

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