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The developmental origins of well-being

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Low birthweight is now known to be associated with increased rates of coronary heart disease and the related disorders, stroke, hypertension and adult-onset diabetes. These associations have been extensively replicated in studies in different countries and are not the result of confounding variables. They extend across the normal range of birthweight and depend on lower birthweights in relation to the duration of gestation rather than the effects of premature birth. The associations are thought to be consequences of developmental plasticity, the phenomenon by which one genotype can give rise to a range of different physiological or morphological states in response to different environmental conditions during development. Recent observations have shown that impaired growth in infancy and rapid childhood weight gain exacerbate the effects of impaired prenatal growth. A new vision of optimal early human development is emerging, which takes account of health and well-being throughout life.

Keywords: developmental plasticity; chronic disease; reproductive fitness

1. INTRODUCTION

The recent discovery that people who develop chronic disease grow differently from other people during foetal life and childhood has led to a new 'developmental' model for a group of diseases including coronary heart disease, stroke, high blood pressure and type 2 (adult onset) diabetes (Barker *et al*. 1989). To explore the developmental origins of chronic disease required studies of a kind that had not hitherto been carried out. It was necessary to identify groups of men and women now in middle to late life, whose size at birth had been recorded at the time. Their birthweight could thereby be related to the later occurrence of coronary heart disease and other disorders. In Hertfordshire, UK, from 1911 onwards, women were attended during birth by a midwife, who recorded the birthweight. A health visitor went to the baby's home at intervals throughout infancy, and the weight at 1 year was recorded. Table 1 shows the findings in 10 636 men born between 1911 and 1930, inclusive. Standardized mortality ratios for coronary heart disease fell with increasing birthweight. There were stronger trends with the weight at 1 year. The association between low birthweight and coronary heart disease has now been replicated among men and women in Europe, the USA and India (Osmond *et al.* 1993; Frankel *et al.* 1996; Stein *et al.* 1996; Rich-Edwards *et al.* 1997; Leon *et al.* 1998; Eriksson *et al.* 2001). Low birthweight has been shown to predict type 2 diabetes in studies from around the world (Hales *et al.* 1991; McCance *et al.* 1994; Lithell *et al.* 1996; Rich-Edwards *et al.* 1999; Forsén *et al.* 2000).

These findings suggest that influences linked to early growth have an important effect on the risk of coronary heart disease and type 2 diabetes. It has been argued, however, that people whose growth was impaired *in utero* and during infancy may continue to be exposed to an adverse environment in childhood and adult life, and it is this later environment that produces the effects attributed to intrauterine influences. There is now strong evidence that this argument cannot be sustained (Frankel *et al.* 1996; Rich-Edwards *et al.* 1997; Leon *et al.* 1998). The associations between low birthweight and later disease have been shown to be independent of influences such as socioeconomic status and cigarette smoking, though adult lifestyle adds to the effects of early life: for example, the prevalence of type 2 diabetes is highest in people who had a low birthweight and became obese as adults (Hales *et al.* 1991; McCance *et al.* 1994; Lithell *et al.* 1996; Rich-Edwards *et al.* 1999; Forsén *et al.* 2000).

2. BIOLOGICAL BASIS

During development, the organs and systems of the body go through sensitive periods when they are plastic and sensitive to the environment. For most organs and systems, the sensitive period occurs *in utero*. Developmental plasticity enables the production of phenotypes that are better matched to their environment than would be possible if the same phenotype were produced in all environments (West-Eberhard 1989; Bateson & Martin 1999). If a mother is poorly nourished, the baby responds by adaptations, such as reduced body size and altered metabolism, which help it to survive. Because, as Mellanby (1933) noted long ago, the ability of a human mother to nourish her baby is partly determined by her own experience *in utero*, and by her childhood growth, the human foetus responds not only to conditions at the time of the pregnancy but also to conditions occurring potentially several decades before. Until recently, we have overlooked a growing body of evidence that systems of the body that are closely related to adult disease, such as the regulation of blood pressure, are also

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Table 1. Hazard ratios (95% confidence intervals) for death from coronary heart disease according to birthweight and weight at 1 year in 10 636 men born in Hertfordshire between 1911 and 1930, inclusive.

	death from coronary heart disease	
weight (pounds (kg))	before 65 years	all ages
birthweight		
$\leqslant$ 5.5 (2.5) ($n = 486$)	1.50 (0.98–2.31)	1.37 (1.00–1.86)
5.5–6.5 (2.9) ($n = 1385$)	1.27 (0.89–1.83)	1.29 (1.01–1.66)
6.5–7.5 (2.9–3.4) ($n = 3162$)	1.17 (0.84–1.63)	1.14 (0.91–1.44)
7.5–8.5 (3.4–3.9) ($n = 3308$)	1.07 (0.77–1.49)	1.12 (0.89–1.40)
8.5–9.5 (3.9–4.3) ($n = 1564$)	0.96 (0.66–1.39)	0.97 (0.75–1.25)
$>$ 9.5 (4.3) ($n = 731$)	1.00	1.00
p for trend	0.001	0.005
1 year old		
$\leqslant$ 18 (8.2) ($n = 715$)	2.22 (1.33–3.73)	1.89 (1.34–2.66)
18–20 (8.2–9.1) ($n = 1806$)	1.80 (1.11–2.93)	1.58 (1.15–2.16)
20–22 (9.1–10.0) ($n = 3404$)	1.96 (1.23–3.12)	1.66 (1.23–2.25)
22–24 (10.0–10.9) ($n = 2824$)	1.52 (0.95–2.45)	1.36 (1.00–1.85)
24–26 (10.9–11.8) ($n = 1391$)	1.36 (0.82–2.26)	1.29 (0.93–1.78)
$>$ 26 (11.8) ($n = 496$)	1.00	1.00
p for trend	$<$ 0.001	$<$ 0.001

plastic during early development. In animals it is surprisingly easy to produce lifelong changes in the blood pressure and metabolism of offspring by minor modifications to the diet of the mother before and during pregnancy (Widdowson & McCance 1963; Kwong *et al.* 2000).

The different sizes of newborn human babies exemplifies this plasticity. The growth of babies has to be constrained by the size of the mother, otherwise normal birth could not occur. Small women have small babies: in pregnancies after ovum donation small women have small babies even if the woman donating the egg is large (Brooks *et al.* 1995). Babies may be small because their growth is constrained by maternal size or because they lack the nutrients for growth. As McCance wrote, 'the size attained *in utero* depends on the services which the mother is able to supply. These are mainly food and accommodation' (McCance 1962). A mother's height or bony pelvic dimensions are generally not found to be important predictors of the baby's long-term health, and research into the developmental origins of disease has focused on the nutrient supply to the baby, while recognizing that other influences such as hypoxia and stress also influence foetal growth. This focus on foetal nutrition was endorsed in a recent review (Harding 2001). Although the growth of a foetus is influenced by its genes, studies in humans and animals show that it is usually limited by the nutrients it receives (Barker 1998; Harding 2001). Around the world, size at birth in relation to gestational age is a marker of foetal nutrition. In developing countries many babies are undernourished because their mothers are chronically malnourished. Despite current levels of nutrition in western countries, the nutrition of many foetuses and infants remains sub-optimal, because the nutrients available are unbalanced or because their passage to the foetus is constrained by the long and vulnerable foetal supply line.

3. DEVELOPMENTAL ORIGINS HYPOTHESIS

The developmental (or foetal) origins hypothesis proposes that coronary heart disease, type 2 diabetes, stroke and hypertension originate through developmental plasticity, in response to undernutrition during foetal life and infancy (Barker 1995; Barker *et al.* 2002*a*). Why should foetal responses to undernutrition lead to disease in later life? The general answer is clear. According to 'life-history theory', increased allocation of energy to the development of one trait, such as brain growth, necessarily reduces its allocation to one or more other traits, such as tissue repair processes. Smaller babies, who have had a lesser allocation of energy, must incur higher costs, and these it seems include disease in later life. A more specific answer to the question is that people who were small at birth are vulnerable to later disease through at least three kinds of processes. First, they have fewer cells in key organs, such as the kidney. This may be as a result of a general reduction in cell numbers or a selective one: undernourished babies may, for example, divert blood flow away from the trunk to protect the brain. One theory holds that high blood pressure is initiated by the reduced number of glomeruli in the kidneys of people who were small at birth (Brenner & Chertow 1993). Such a reduced number necessarily leads to an increased blood flow through each glomerulus. Over time, this hyperfiltration may lead to the development of glomerulo-sclerosis which, combined with the loss of glomeruli that accompanies normal ageing, results in accelerated age-related loss of glomeruli and a self-perpetuating cycle of rising blood pressure and glomerular loss. Direct evidence in support of this hypothesis has come from a study of the kidneys of people killed in road accidents. Those being treated for hypertension had fewer but larger glomeruli (Keller *et al.* 2003; Ingelfinger 2003).

Another process by which slow foetal growth may be linked to later disease is in the setting of hormones and metabolism. An undernourished baby may establish a 'thrifty' way of handling food (Hales & Barker 1992). Tissue resistance to the effects of insulin, which underlies type 2 diabetes and is associated with low birthweight, may be viewed as the persistence of a foetal response by which glucose concentrations are maintained in the blood for the benefit of the brain, but at the expense of glucose transport into the muscles and muscle growth (Phillips 1996).

Table 2. Hazard ratios (95% confidence intervals) for coronary heart disease in 3676 men according to ponderal index at birth (birthweight/length^3) and taxable income in adult life.

	ponderal index at birth	
household income in pounds sterling per year	$\leqslant$ 26.0 kg/m^3 ($n = 1475$)	$>$ 26.0 kg/m^3 ($n = 2154$)
$>$ £15 700	1.00	1.19 (0.65–2.19)
£12 400–£15 700	1.54 (0.83–2.87)	1.42 (0.78–2.57)
£10 700–£12 400	1.07 (0.51–2.22)	1.66 (0.90–3.07)
£8 400–£10 700	2.07 (1.13–3.79)	1.44 (0.79–2.62)
$\leqslant$ £8400	2.58 (1.45–4.60)	1.37 (0.75–2.51)
p for trend	< 0.001	0.75

A third link between low birthweight and later disease is that people who were small at birth are more vulnerable to adverse environmental influences in later life. Observations of animals show that the environment during development can permanently change not only the body's structure and function but also its responses to environmental influences encountered in later life (Bateson & Martin 1999). Table 2 shows the association between low income in adult life on coronary heart disease among men in Helsinki (Barker *et al.* 2001). As expected, men who had a low taxable income had higher rates of the disease. There is no agreed explanation for this, but the higher rates of coronary heart disease among poorer people is a feature of the disease in western countries and a major component of the social inequalities in health. Among the men in Helsinki, this association was confined to those who had had slow foetal growth and were thin at birth, defined by a ponderal index (birthweight/length^3) of less than 26 kg/m^3 (table 2). Around one-quarter of all baby boys born in Britain today are thin under this definition. Men who were not thin at birth were resilient to the effects of low income on coronary heart disease.

One explanation of these findings emphasizes the psychosocial consequences of a low position in the social hierarchy, as indicated by low income and social class, and suggests that perceptions of low social status and lack of success lead to changes in neuroendocrine pathways and hence to disease (Marmot & Wilkinson 2001). The findings in Helsinki seem consistent with this. People who are small at birth are known to have persisting alterations in responses to stress, including raised serum cortisol concentrations (Phillips *et al.* 2000). It has been suggested that persisting small elevations of cortisol concentrations over many years may have effects similar to those seen when tumours lead to more sudden, large increases in glucocorticoid concentrations. People with Cushing's syndrome are insulin resistant and have raised blood pressure, both of which predispose them to coronary heart disease.

4. CHILDHOOD GROWTH AND CHRONIC DISEASE

Figure 1 shows the growth of 357 men who were either admitted to hospital with coronary heart disease or died from it (Eriksson *et al.* 2001). They belong to a cohort of 4630 men who were born in Helsinki, and their growth is expressed as standard deviation scores, termed *Z*-scores. The *Z*-score for the cohort is set at zero, and a boy maintaining a steady position as large or small in relation to other boys would follow a horizontal path on the figure. Boys who later developed coronary heart disease, however, were small at birth, remained small in infancy but had accelerated gain in weight and body-mass index (weight/height^2) thereafter. By contrast, their heights remained below average. As in Hertfordshire, the hazard ratios for coronary heart disease fell with increasing weight at 1 year, and also with increasing length and, more strongly, with body-mass index (weight/height^2). A small size at this age predicted coronary heart disease independently of size at birth. Hence there appear to be at least two pathways of development that lead to coronary heart disease among men. One begins with slow growth *in utero* and low birthweight and thinness at birth, thought to be a consequence of foetal undernutrition. The other begins with poor weight gain during infancy, which occurs in babies born into poor living conditions with overcrowding and consequent recurrent minor illness. Among the 4130 girls in the same birth cohort, the 87 who later developed coronary heart disease showed a broadly similar pattern of growth to the boys (Forsén *et al.* 2004). They were, however, short at birth rather than thin but became thin during infancy. This persisted up to the age of 4 years, after which they gained weight rapidly. In both sexes, disease risk is related to the tempo of weight gain during childhood rather than to body size at any particular age. As D'Arcy Thompson wrote in 1917, 'to say that children of a given age vary in the rate at which they are growing would seem to be a more fundamental statement than that they vary in the size to which they have grown' (Thompson 1942).

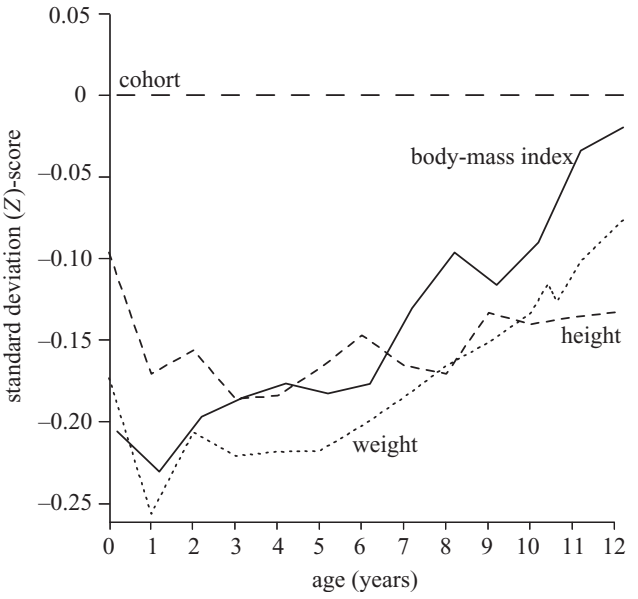

Figure 1. Mean standard deviation scores (*Z*-scores) for height, weight and body-mass index during childhood, in 357 boys who later developed coronary heart disease within a cohort of 4630 boys. At any age, the mean *Z*-score for the cohort is set at 0, while the standard deviation is set at 1.

High blood pressure and type 2 diabetes are associated with the same general pattern of growth as coronary heart disease. In both sexes, the risk of disease falls with increasing birthweight and rises with rapid weight gain in early childhood (Hales *et al.* 1991; McCance *et al.* 1994; Curhan *et al.* 1996; Lithell *et al.* 1996; Rich-Edwards *et al.* 1999;

Table 3. Odds ratios (95% confidence intervals) for high blood pressure (2997 cases) according to birthweight and body-mass index at 11 years among 13 517 men and women.
(Odds ratios adjusted for sex and year of birth.)

	body-mass index at 11 years (kg/m^2)			
birthweight (kg)	< 15.7	15.7–16.6	16.6–17.6	> 17.6
⩽ 3.0	2.0 (1.3–3.2)	1.9 (1.2–3.1)	1.9 (1.2–3.0)	2.3 (1.5–3.8)
3.0–3.5	1.7 (1.1–2.6)	1.9 (1.2–2.9)	1.9 (1.2–3.0)	2.2 (1.4–3.4)
3.5–4.0	1.7 (1.0–2.6)	1.7 (1.1–2.6)	1.5 (1.0–2.4)	1.9 (1.2–2.9)
> 4.0	1.0	1.9 (1.1–3.1)	1.0 (0.6–1.7)	1.7 (1.1–2.8)

Forsén *et al.* 2000). Table 3 shows hazard ratios for hypertension, defined as high blood pressure requiring treatment, according to birthweight and quarters of body-mass index at age 11 years among men and women born in Helsinki between 1924 and 1944, inclusive (Barker *et al.* 2002*a*). At any birthweight, hazard ratios tend to be highest in people who had a high childhood body-mass index. Conversely, at any childhood body mass, the hazard ratios are highest among those who had low birthweight.

There is a substantial literature showing that birthweight is associated with differences in blood pressure within the normal range (Huxley *et al.* 2000). These differences are found in children and adults but they tend to be small. A 1000 g (2.2 pounds) difference in birthweight is associated with *ca*. 3 mm Hg difference in systolic pressure. The contrast between this small effect and the large effect on hypertension (table 3) suggests that lesions accompanying poor foetal growth and tending to elevate blood pressure, which may include a reduced number of glomeruli, have a small influence on blood pressure within the normal range because counter-regulatory mechanisms maintain normal blood pressure levels. As described already (see § 3), a reduced number of glomeruli leads to an increased blood flow through each glomerulus. Experience in renal transplantation surgery shows that such hyperfiltration is greatest in people with a large body size, and these people are the most vulnerable to the development of glomerulosclerosis and consequent glomerular destruction. This may explain why high childhood body-mass index is deleterious (table 3). Ultimately, homeostasis can no longer be maintained and blood pressure rises, which accelerates glomerular destruction. A cycle of rising blood pressure, further glomerular destruction and further rise in blood pressure may be initiated (Brenner & Chertow 1993). Evidence to support the development of self-perpetuating cycles comes from a study of elderly people in Helsinki among whom the effect of birthweight on blood pressure was confined to those being treated for high blood pressure (Ylihärsilä *et al.* 2003). Despite their treatment, the blood pressures of those who had low birthweight were markedly higher. There was a difference of more than 20 mm Hg in systolic pressure between those who weighed 2500 g (5.5 pounds) or less at birth and those who weighed 4000 g (8.8 pounds) or more. Among the normotensive subjects, birthweight was unrelated to blood pressure. An inference is that by the time they reached old age, most of the people with lesions acquired *in utero* had developed clinical hypertension.

Table 4 shows the relation between age at 'adiposity rebound' and later type 2 diabetes (Eriksson *et al.* 2003*a*). After the age of 2 years the degree of obesity of young children, as measured by body-mass index, decreases to a minimum *ca*. 6 years of age before increasing again: the so-called adiposity rebound. The age at adiposity rebound ranges from *ca*. 3 years to 8 years or more. Table 4 shows that early adiposity rebound is strongly related to a high body-mass index in later childhood, as has previously been shown (Rolland-Cachera *et al.* 1987). It also predicts an increased incidence of type 2 diabetes in later life. The incidence of later type 2 diabetes was 8.6% in children whose adiposity rebound occurred at 4 years of age or less, falling to 1.8% in children whose body-mass index did not start to increase until 8 years or more. This large difference emphasizes the importance of the tempo of childhood weight gain. The association between early adiposity rebound and impaired glucose tolerance has recently been replicated in a longitudinal study in Delhi, India (Bhargava *et al.* 2004). In both studies, an early adiposity rebound was found to be associated with thinness at birth and at 1 year. It is not therefore the young child who is overweight who is at greatest risk of type 2 diabetes, but the one who is thin but subsequently gains weight rapidly. Little is known about the physiological or environmental influences that determine the age at adiposity rebound.

5. COMPENSATORY GROWTH

When undernutrition during early development is followed by improved nutrition, many animals and plants stage accelerated or 'compensatory' growth. Compensatory growth has costs, however, which in animals include reduced lifespan (Metcalfe & Monaghan 2001). There are a number of processes by which, in humans, undernutrition and small size at birth followed by rapid childhood growth could lead to cardiovascular disease and type 2 diabetes in later life (Forsén *et al.* 2000; Eriksson *et al.* 2001; Barker *et al.* 2002*a*). Rapid growth may be associated with persisting hormonal and metabolic changes. Larger body size may increase the functional demand on functional capacity that has been reduced by slow early growth: fewer glomeruli, for example. Rapid weight gain may lead to an unfavourable body composition. Babies that are small and thin at birth lack muscle, a deficiency that will persist because the critical period for muscle growth occurs *in utero* and there is little cell replication after birth (Widdowson *et al.* 1972). If they develop a high body mass during later childhood they may have a disproportionately high fat mass in relation to lean body mass, which will lead to insulin resistance (Eriksson *et al.* 2002*a*).

Table 4. Body mass index at 11 years of age and cumulative incidence of type 2 diabetes according to age at adiposity rebound in 8760 men and women.
(Figures in parentheses are numbers of subjects.)

	mean body-mass index (kg/m^2) at age 11	cumulative incidence of diabetes (% (*n*))		
age at adiposity rebound (years)	all	men	women	all
$\leqslant 4$	19.7	8.1 (86)	8.9 (112)	8.6 (198)
5	17.6	6.2 (904)	2.5 (864)	4.4 (1768)
6	17.0	3.7 (1861)	2.5 (1456)	3.2 (3317)
7	16.8	2.4 (249)	2.1 (243)	2.2 (492)
$\geqslant 8$	16.7	3.0 (135)	0.7 (150)	1.8 (285)
p for trend	< 0.001	< 0.001	0.002	< 0.001

Table 5. Cumulative incidence (%) of hypertension according to birthweight and father's social class in 8760 men and women.

	father's social class			
birthweight (kg)	labourer	lower middle class	upper middle class	*p* for trend
$\leqslant 3.0$	22.2	20.2	10.5	0.002
3.0–3.5	18.8	15.2	10.6	< 0.001
3.5–4.0	14.5	12.5	10.3	0.04
> 4.0	11.1	15.6	15.7	0.11
p for trend	< 0.001	0.05	0.79	

6. PATHWAYS TO DISEASE

New studies, especially those in Helsinki where there is exceptionally detailed information on child growth and socio-economic circumstances, suggest increasingly that the pathogenesis of coronary heart disease, and the disorders related to it, depend on a series of interactions occurring at different stages of development. To begin with, the effects of the genes acquired at conception may be conditioned by the early environment (Dennison *et al.* 2001; Eriksson *et al.* 2002*b*). For example, the Pro12Pro polymorphism of the PPAR-Y gene is known to be associated with insulin resistance. In a study of 476 elderly people in Helsinki, however, this effect was found only among men and women who had low birthweight. Such interactions between the effects of genetic polymorphisms and those of birthweight, a marker of foetal nutrition (Harding 2001), would be predicted if chronic disease originates through developmental plasticity (West-Eberhard 1989; Bateson & Martin 1999).

The effects of the intrauterine environment on later disease are conditioned not only by events at conception, but by events after birth. Table 3 shows how the effects are conditioned by childhood weight gain. Table 2 shows that the effects of low ponderal index at birth are conditioned by living conditions in adult life. Table 5 shows how the effects of low birthweight on later hypertension are conditioned by living conditions in childhood, as indicated by the occupational status of the father which, under a Finnish classification, groups families into three classes (Barker *et al.* 2002*b*). Among all of the men and women, low birthweight was associated with an increased incidence of hypertension, as expected from previous findings (Curhan *et al.* 1996). This association, however, was present only among those who were born into families where the father was a labourer or of lower middle class. Again, this is a statistically strong interaction with the effects of birthweight.

It seems that the pathogenesis of cardiovascular disease and type 2 diabetes cannot be understood within a model in which risks associated with adverse influences at different stages of life are additive. Rather, disease is the product of branching paths of development. The branchings are triggered by the environment. The pathways determine the vulnerability of each individual to what lies ahead. The pathway to coronary heart disease can originate either in slow foetal growth as a consequence of undernutrition, or in poor infant growth as a consequence of poor living conditions. Thereafter the pathway is determined by rates of weight gain in childhood, by socio-economic conditions and, presumably, by other influences as yet undiscovered.

The effects of slow foetal growth and low birthweight, and the effects of post-natal development, depend on environmental influences and paths of development that precede and follow them. Low birthweight, or any other single influence, does not have 'an' effect that is best estimated by a pooled estimate from all published studies. As René Dubos wrote 'the effects of the physical and social environments cannot be understood without knowledge of individual history' (Dubos 1960). Unravelling the causation of chronic disease, and hence the way to prevent it, will therefore require an understanding of heterogeneity.

7. STRENGTH OF EFFECTS

Low birthweight, though a convenient marker in epidemiological studies, is an inadequate description of the phenotypic characteristics of a baby that determine its long-term health. The wartime famine in Holland produced lifelong insulin resistance in babies who were *in utero* at the time, with little alteration in birthweight (Ravelli *et al.* 1998). In babies, as in children, slowing of growth is a response to a poor environment, especially undernutrition, but body size at birth does not adequately describe the long-term morphological and physiological consequences of

undernutrition. The same birthweight can be attained by many different paths of foetal growth, and each is likely to be accompanied by different gene–environment interactions (Harding 2001). Nevertheless, birthweight provides a basis for estimating the magnitude of the effects of the foetal phase of development on later disease, though it is likely to underestimate them.

Because the risk of cardiovascular disease is influenced both by small body size at birth and during infancy and by rapid weight gain in childhood, estimation of the risk of disease attributable to early development requires data on foetal, infant and childhood growth. The Helsinki studies are currently the main source of information (Barker *et al.* 2002*a*). If each man in the cohort had been in the highest third of ponderal index at birth, and each woman in the highest third of birth length, and if each man or woman had lowered their body-mass index between the ages of 3 and 11 years, the incidence of coronary heart disease would have been reduced by 25% in men and 63% in women (Barker *et al.* 2002*a*).

8. SENSITIVE PERIODS

The war-time famine in western Holland began suddenly in November 1944 and ended abruptly six months later when the allied armies liberated the country (Ravelli *et al.* 1998). During the famine, official rations fell to around 700 calories. The subsequent effect on people who were *in utero* at the time depended on the stage of gestation at which they were exposed to the famine. People who were conceived during the famine now display raised serum cholesterol and raised rates of coronary heart disease. By contrast, those conceived before the famine but exposed to it in mid-late gestation are insulin resistant and have impaired glucose tolerance (Ravelli *et al.* 1998; Roseboom *et al.* 2001). These differences presumably reflect sensitive periods in the development of organs such as the liver, heart and muscle occurring at different stages of foetal development. The effects of growth failure at different phases of infancy also depend on its timing. Type 2 diabetes is associated with a failure of linear growth between birth and three months of age, which may coincide with a sensitive period of development for insulin production by the endocrine pancreas (Eriksson *et al.* 2003*b*).

9. WELL-BEING

Most of the data that link development with later health, and hence well-being, come from studies of disease. Underlying the associations between early growth and later disease, however, are processes that are likely to affect the well-being of people who are, from a medical viewpoint, healthy. People who were small at birth have heightened stress responses (Phillips *et al.* 2000), one manifestation of lifelong settings of hormones and metabolism that are established before birth. These settings affect reproductive physiology, as is well known in animals (Barraclough 1961; Barker 1998). In Hertfordshire, men who were small at birth are less likely to marry, an observation confirmed in Sweden (Phillips *et al.* 2001). Around 20% of men who weighed 2500 g (5.5 pounds) or less at birth remained unmarried in middle age compared with only 5% in men weighing 3500 g (7.75 pounds) or more. This is not an effect of adult height: at any height those who were smaller at birth were less likely to marry. It seems that restriction of growth before birth alters some aspect of partner selection: sexuality, socialization, personality or emotional responses.

Women born after term tend to have altered gonadotrophin production and polycystic ovaries (Cresswell *et al.* 1997). A possible explanation is that the human foetus produces large amounts of androgens, which are converted to oestrogen by the placenta and pass to the maternal circulation. Placental failure associated with postmaturity could expose the foetal hypothalamus to increased concentrations of androgens or oestrogens and alter hypothalamic–pituitary set points for the release of luteinizing hormone. Further evidence that a woman's reproductive fitness may be influenced *in utero* comes from studies of age at menarche. In a national sample of British girls, those who reached menarche at the youngest age had low birthweight but put on weight rapidly in childhood (Cooper *et al.* 1996). Similar findings came from a study of Filipino girls (Adair 2001). Again, the suggested link between foetal growth and age at menarche is the setting of the pattern of gonadotrophin release. Pulsatile release of luteinizing and follicle stimulating hormone is initiated *in utero*, continues through infancy, and thereafter ceases until it resumes at puberty.

In the Hertfordshire study, men and women who committed suicide, which is commonly the result of depression, had low weight gain in infancy (Barker *et al.* 1995). Although this could be a result of adverse psycho–social influences in infancy, there is nothing in the Hertfordshire records that supports this, and it raises the possibility that adult depression is initiated by *in utero* setting of hormonal axes which influence growth in infancy and mood in later life. Patients with depression have been found to have an abnormal secretion of growth hormone and abnormalities in the hypothalamic–adrenal and hypothalamic–thyroid axes (Checkley 1992).

10. CONCLUSION

The list of chronic diseases whose origins lie in early development extends beyond cardiovascular disease and type 2 diabetes. For example, there is now strong evidence that osteoporosis is another of the body's 'memories' of undernutrition at a sensitive early stage of development (Cooper *et al.* 2002). The demonstration that normal variations in foetal size at birth have implications for health throughout life has prompted a re-evaluation of foetal development. There is increasing evidence that a woman's own foetal and childhood growth, and her diet and body composition at the time of conception as well as during pregnancy, play an important role in determining the lifelong well-being of her children.

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