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Developmental Origins of Health and Disease

This landmark publication provides the first definitive account of how and why subtle influences on the fetus and during early life can have such profound consequences for adult health and diseases. Although the epidemiological evidence for this link has long proved compelling, it is only much more recently that the scientific basis for this has begun to be studied in depth and fully understood. This compilation, written by many of the world's leading experts in this exciting field, summarises these basic and clinical advances. The link between early development and the onset of many chronic diseases such as coronary heart disease, diabetes and osteoporosis also raises important public health issues. Another fascinating theme in the book concerns evolutionary developmental biology and how the 'evo-devo' debate can cast light on these concepts. Clinicians and basic scientists alike will find this an authoritative book about this exciting and emerging field.

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Developmental Origins of Health and Disease

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Preface

This book could not have been written ten years ago. In the first instance, the field it covers, that of developmental origins of health and disease (DOHaD) was at that stage embryonic and highly controversial. While there was compelling epidemiological data, there was a lack of experimental and mechanistic data on which to create consensus. But over the last decade the science of DOHaD has advanced rapidly. The epidemiological evidence for the DOHaD paradigm is now strongly supported by prospective clinical data, experimental observations and a growing understanding of the underlying molecular and developmental mechanisms. Further, the scope of physiological systems that may be involved has expanded. The relevance of the phenomenon to the ecology of human disease in different populations is now much clearer.

So there is now a pressing need for a book such as this. By the time of its publication, three world congresses on DOHaD will have occurred; an international learned society has been formed; and there are a substantial number of reviews on many aspects of the field and its implications. Yet to date there is no definitive textbook. Students, clinicians and researchers need a volume that brings current knowledge together, whether to introduce them to the subject as a whole or to help them broaden their knowledge of an expanding field.

Moreover, the implications of the DOHaD concept are now becoming clear. The scientific implications now extend not only into epidemiology, developmental biology and physiology, but also into evolutionary biology and anthropology. DOHaD has very
important implications for public health policy, not only in developed but also in developing societies.

In this volume, we have assembled contributions from undisputed experts in the DOHaD field. Many are architects of the ideas that are reviewed throughout. We are enormously grateful to them for their timely and well constructed contributions to the volume. Our thanks must also go to Peter Silver, who commissioned the volume from Cambridge University Press, and to Deborah Peach, Cathy Pinal and Karen Goldstone who worked so hard on the preparation of the manuscripts for publication.
The concept of developmental origins of health and disease (DOHaD) grew from the earlier concept of fetal origins of adult disease (FOAD) (reviewed in Barker 1995, 1998). There are two important reasons for the change. The first results from the large amount of research (much of it reviewed in this book) showing that the early life events which determine in part the risk of later disease occur not only in the fetal period specifically, but throughout the plastic phase of development. In this respect the use of the word ‘development’ is helpful because it implies not only effects operating during early stages of embryonic life (usually the preserve of developmental biology) but also those in infancy. Secondly, the DOHaD terminology emphasises that this area of science has implications not only for disease, and its prevention, but also for health promotion. The latter is of great importance in public health and education programmes in many parts of the world. But the accent on ‘developmental origins’ is more than just a flag of convenience under which several disciplines may sail: it represents a fundamental shift in thinking about the way in which early life processes affect later health and disease in humans.

Previously, proponents of FOAD championed the view that prenatal events were of utmost importance. Adopting this position was tactically necessary in the battle (now won) to gain widespread recognition that the aetiology of many chronic diseases, such as coronary heart disease (Barker and Osmond 1986), type 2 diabetes (Ravelli et al. 1998) or osteoporosis (Cooper et al. 2002), lay not only in genetic predisposition or in adult lifestyle, but also in the ways in which early life events could affect subsequent biology. As a result, both epidemiologists and experimentalists have expanded the period of interest to that around conception (Cnattingius et al. 1998, Kwong et al. 2000, Inskip et al. 2001, Bloomfield et al. 2003, Robinson et al. 2004, Crozier et al. in press). In parallel, other clinical and basic scientists were stressing the importance of the postnatal environment during suckling, infancy and childhood in setting an individual on the path to health or disease (Eriksson et al. 1999, 2003, Singhal et al. 2002, 2003). At times, these two schools of thought appeared to be at loggerheads, and the resulting conflict did little to promote understanding of the importance of the field that they shared. Development is a continuum extending on either side of birth – consider the wide variation in maturation at birth in different species. More recently, the recognition that the field of evolutionary developmental biology (‘evo-devo’) has enabled the development of a broader understanding of the phenomenon and, in turn, studies of the DOHaD phenomenon have led to new concepts in evo-devo biology. Both these advances in theoretical thinking and new experimental observations allow recognition that both pre- and postnatal environmental factors play vitally important roles, and that what matters most is the degree of match/mismatch between...
them. This idea is more fully explained in Chapter 3. Suffice it to say here that the term ‘development’ helps to emphasise the importance of this continuity.

There are other ways in which the epidemiological work has continued to be controversial. The early concerns about confounding variables led to discussion on the relative importance of low birthweight versus other contributory factors. At times such discussions became rather sterile. Because the consensus in both animal and human research is now that phenotypes can be induced in offspring without necessarily being accompanied by low birthweight, it is clear that reduction of fetal growth per se does not lie on a causal pathway to later disease. Rather, low birthweight is a surrogate marker of the effects of the prenatal environment on the fetus, and one aspect of the fetal ‘coping’ responses to that environment. The problems in this area were compounded by an insufficient appreciation of the distinction between clinically manifest disease and other surrogate markers or risk factors for disease (Huxley et al. 2002). Examples included the use of elevated blood pressure as a marker for cardiovascular disease, or reduced insulin sensitivity as a marker of diabetes. With the wisdom of hindsight, it is not surprising that interpretation of the links between surrogates of fetal adaptation (birthweight) and later disease (blood pressure, insulin sensitivity) yielded different interpretations at the hands of different researchers. As the field has progressed, however, we have developed more sensitive markers of fetal adaptive responses and these can now directly relate to clinical disease. When this is done, the striking correlations that underpin the DOHaD hypothesis begin to emerge.

The work conducted by basic scientists, many of them using experimental animals, has not been without criticism either. Inevitably the use of a range of species to investigate the phenomenon, partly based on convenience, cost and suitability for experimental techniques, has produced a similarly sterile discussion about which provides the most suitable experimental model for the human (Symonds et al. 2000, Langley-Evans 2000, Bertram and Hanson 2001, Armitage et al. 2004). Ideas have become refined as confirmation of similar aspects of the phenomenon across species has been made. Surprisingly, one of the features to emerge from the intense research activity in the area is how easy it is to manipulate the phenotype of offspring by changes in the early environment. This poses the problem of the relevance to humans of an observation made in animals. A key issue is to distinguish between factors that disrupt development and which are not regulated and those that are based on the processes of developmental plasticity and may have adaptive value – these ideas are expanded in Chapter 3. We have to accept that some environmental exposures, either clinical or experimental, simply disrupt the normal pattern of development. Such exposures do not necessarily lead to increased risk of disease (which cannot usually be ascertained in animals), nor have direct relevance to DOHaD in humans.

Notwithstanding these issues, studies in animals have revealed exciting insights into the mechanisms which underlie DOHaD. The first has been referred to above, and is the perception that changes in the developmental environment can induce phenotypic changes which are not necessarily accompanied by a reduction of birthweight or change in body proportions at birth (Hanson 2002). But perhaps the most exciting development relates to the area of gene–environment interactions, usually now referred to as epigenetics. As the reader will see (Chapter 5), it is now clear that graded changes in certain factors, such as histone acetylation and the degree of DNA methylation (Weaver et al. 2004), can produce subtle changes in the expression of genes. Coupled with our increasing knowledge about post-transcriptional and post-translational factors which influence gene expression, we are now beginning to see how developmental plasticity operates through environmental actions interceding between the genotype and the induction of the phenotype. Because such epigenetic processes depend on dietary availability of key nutrients and micronutrients, and because they can be affected by hormone levels (Waterland and Jirtle 2004), they are prime candidates for mechanisms underlying DOHaD, at least as regards the most commonly studied systems.
Moreover, whilst it was formerly thought that the methylation of DNA was established anew in the embryo at or before the blastocyst stage, it is now clear that levels of methylation can to a degree be transmitted from one generation to the next (Weaver et al. 2004). Research has revealed several ways in which transgenerational effects can be passed not only from the mother to her offspring but also to her grandchildren and possibly further down the lineage (Drake and Walker 2004).

In Chapter 3 we present a theoretical basis for the DOHaD phenomenon, in the context of previous theories that contribute substantially to it, such as metabolic teratogenesis, the thrifty genotype, thrifty phenotype and others. We believe that such an exercise is important for synthesising current ideas and allowing the incorporation of new experimental findings. It is surprising how easily current experimental findings fit into such a theory, but its real utility will probably be derived when a set of observations which do not fit is uncovered. In this sense using a theory makes the identification of such extraneous observations easier, and goes on to generate new experimental approaches, hypotheses and, ultimately, new theories. Even as it stands, however, the theory must ask questions about our tacit assumption that neo-Darwinian processes have contributed greatly to phenotypic diversity, including phenotypes susceptible to disease, in human populations. We think the implications of theoretical thinking regarding DOHaD for evolutionary biology will be substantial.

Most research in the field has been focused on metabolic disorders or on the cardiovascular system, reflecting the original epidemiological observations of Barker and his colleagues. Indeed, many of the chapters in this book reflect this emphasis. But now research in DOHaD is broadening to include other chronic diseases, such as osteoporosis (Cooper et al. 2002), cognitive decline (Richards et al. 2002, Gale et al. 2003), behavioural abnormalities (Thompson et al. 2001, Wahlbeck et al. 2001), obesity (Eriksson et al. 2001) and some forms of cancer (Dos Santos et al. 2004; see also Chapter 31). This does not mean that the phenomenon is so broad and all-encompassing as to be meaningless. Rather it suggests that an entirely new way of viewing chronic disease will have to be developed in both developed and developing societies. The importance of this to public health policy makers is discussed in Chapter 34.

Many of the contributors to this volume make reference to the importance of the DOHaD concept to public health policy. Various estimates have been made of the impact of early-life factors in determining later risk of disease. A conservative estimate, based on the effects of low birthweight on later endothelial function in childhood, suggests that such early-life programming is equivalent in magnitude to the effect of smoking in later life (Leeson et al. 2001). More dramatic figures come from the retrospective studies of the Helsinki cohort (Chapters 3 and 15) which indicate that men who had a low ponderal index at birth and a high body mass index at age 12 had a five-fold greater risk of dying of coronary heart disease. In relation to the epidemic of obesity and associated diseases, data from India (Bhargava et al. 2004) suggest that the incidence of type 2 diabetes in adults who had an accelerated adiposity rebound as children will be about 25%. More work to define the magnitude of these effects is urgently needed.

Western societies are now characterised by increasing longevity, and this means that the number of those suffering from heart disease and related disorders will increase over the next few years, even though paradoxically those dying from such diseases will fall. There is no room for complacency in the latter statistic, as it may well be only temporary. Furthermore, there is increased interest in the effects of infection and inflammatory responses in early life in contributing to the increased longevity, but there are clearly many factors of equal importance. In earlier life the DOHaD concept is giving important insights into the epidemic of obesity developing in childhood and adolescence (see Chapter 18). The recognition that fat deposition (Vickers et al. 2000, Symonds et al. 2004), propensity to exercise (Vickers et al. 2003) and even dietary preference (Bellinger et al. 2003) may be programmed in early life now
makes it essential to think how to intervene. It is possible that ‘lifestyle’ interventions may be effective in developed societies, in a way that may be less so in developing societies (see Chapter 3). However, even if this is the case it is likely that there will have to be a shift away from public health messages aimed at targeting the population as a whole towards more individually ‘customised’ dietary and exercise plans for those at risk. This will not be easy; the perception that the risk of later disease may be less in the infant who is fat and becomes obese as a young adolescent, in contrast to the small baby who later becomes fat, raises important issues of interpretation. These two children in their teens may in the end have identical body mass indices, but have arrived at that point by different paths and, hence, in later life have very different prospects for disease risk.

Many other factors contribute to the importance of DOHaD in the social policy arena. In particular, family size is decreasing in both industrialised/developed and developing nations. In industrialised societies, this may reflect the tendency for women to pursue careers and to start families later, and reflect social policy as in China with a ‘one child’ policy to limit population size. Moreover, well-meaning programmes to promote contraception accessibility in many developing countries will serve to limit family size further. Because of the maternal-constraint issues raised in Chapter 3, these initiatives may make the mismatch between the pre- and postnatal environments greater.

Our overall conclusion, therefore, is that environmental factors acting during the phase of developmental plasticity interact with genotypic variation to change the capacity of the organism to cope with its environment in later life. Because the postnatal environment can change dramatically, whereas the intrauterine environment is relatively constant over generations, it may well be that much of humankind is now living in an environment beyond that for which we evolved. The DOHaD phenomenon can explain how this manifests in the ecological patterns of human disease. It is no longer possible for adult medicine to ignore the developmental phase of life.

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The ‘developmental origins’ hypothesis: epidemiology

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Introduction

Research worldwide has established that people who were small at birth and had poor growth in infancy have an increased risk of adult coronary heart disease and type 2 diabetes, particularly if this is followed by increased childhood weight gain. There is also evidence linking impaired early growth with other degenerative disorders in later life, including stroke, hypertension, obesity, osteoporosis, obstructive airways disease, reduced cognitive function and poor mental health. The relations between smaller infant size and an increased risk of ill health and adult disease extend across the normal range of infant size in a graded manner. Moreover, recent animal studies and epidemiological data have demonstrated that while maternal thinness and unbalanced diet during pregnancy may have modest effects on size at birth, they are nonetheless associated with raised blood pressure and altered glucose–insulin metabolism and stress responsiveness in the adult offspring. It is now clear that the associations do not simply reflect genetic influences; rather the findings indicate that interactions between the genetic influences and the early-life environment determine disease and susceptibility to adverse influences in the adult environment.

The observations have led to the hypothesis that cardiovascular disease, type 2 diabetes, osteoporosis and obstructive airways disease originate through developmental plastic responses made by the fetus and infant as part of a prediction of the subsequent environment to which it anticipates that it will be exposed. Critical periods in development result in irreversible changes; if the environment in childhood and adult life differs from that predicted during fetal life and infancy, the developmental responses may increase the risk of adult disease. This chapter provides an overview of some of the epidemiological evidence underpinning the developmental origins of degenerative disease. Evidence is also accumulating indicating important developmental influences on cancer, described in Chapter 31.

Fetal, infant and childhood growth in relation to health in later life

Ecological observations pointing to developmental influences on adult health

At the start of the twentieth century the incidence of coronary heart disease rose steeply in western countries so that it became the most common cause of death. In many of these countries the steep rise has been followed by a fall over recent decades that cannot be accounted for by changes in adult lifestyle. The incidence of coronary heart disease is now rising in other parts of the world to which western influences...
A clue suggesting that coronary heart disease might originate during fetal development came from studies of death rates among babies in Britain during the early 1900s (Barker 1998). Perinatal mortality rates differed considerably between one part of the country and another, being highest in some of the northern industrial towns and the poorer rural areas in the north and west. This geographical pattern in death rates was shown to closely resemble today’s large variations in death rates from coronary heart disease (Barker 1998). The usual certified cause of death in newborn babies during the early 1900s was low birthweight, and one possible conclusion suggested by the geographical association was that low rates of growth before birth are in some way linked to the development of coronary heart disease in adult life. Although it had previously been suggested that events in childhood influence the pathogenesis of coronary heart disease, the hypothesis that influences during fetal life and infancy play a critical role provided a new focus for research.

Coronary heart disease

Cohort studies of size at birth and coronary heart disease

The first direct evidence that an adverse intrauterine environment might have long-term consequences for the risk of coronary heart disease came from follow-up studies of men and women in middle and late life whose body measurements at birth had been recorded. A study of people born in Hertfordshire, UK, showed for the first time that those who had had low birthweights had increased death rates from coronary heart disease in adult life (Osmond et al. 1993, Barker 1998). Thus, among 15 726 people born during 1911 to 1930, death rates from coronary heart disease fell progressively with increasing birthweight in both men and women (Fig. 2.1). A small rise at the highest birthweights in men could relate to the macrosomic infants of women with gestational diabetes. Another study, of 1586 men born in Sheffield during 1907 to 1925, showed that it was particularly people who were small at birth as a result of growth
restriction who were at increased risk of the disease (Barker et al. 1993a).

Replication of the UK findings has led to wide acceptance that low rates of fetal growth are associated with coronary heart disease in later life. For example, confirmation of a link between low birthweight and adult coronary heart disease has come from studies of 1200 men in Caerphilly, south Wales (Frankel et al. 1996) and of 70 297 nurses in the United States (Rich-Edwards et al. 1997). The latter study found a two-fold fall in the relative risk of non-fatal coronary heart disease across the range of birthweight. Similarly, among 517 men and women in Mysore, south India the prevalence of coronary heart disease in men and women aged 45 years or older fell from 15% in those who weighed 2.5 kg or less at birth, to 4% in those who weighed 3.2 kg or more (Stein et al. 1996).

Follow-up studies of populations with more detailed birth measurements suggest that altered birth proportions are more strongly associated with late outcomes than is birthweight per se (Forsen et al. 1997). The Hertfordshire records and the nurses and Caerphilly studies did not include measurements of body size at birth other than weight, but in populations where birth length was recorded, derivation of ponderal index (birthweight/length$^3$) allows a crude assessment of body composition and thinness at birth; ponderal index cannot, however, adequately distinguish variations in fat and lean mass. Where neonatal head circumference has also been recorded the baby whose body and trunk is small in relation to its head, as a result of ‘brain sparing’, can also be distinguished. Patterns of altered birth proportions and restricted fetal growth linked with later coronary heart disease may be summarised as a small head circumference, shortness or thinness (Barker et al. 1993a, Martyn et al. 1996a, Forsen et al. 1997, Barker 1998, Eriksson et al. 1999, 2001).

Although low placental weight (Forsen et al. 1997) and an altered ratio of placental weight to birthweight have also been linked with raised adult coronary heart disease death rates (Martyn et al. 1996a, Forsen et al. 1999), other studies have found no association with placental weight (Leon et al. 1998, Eriksson et al. 2001). Animal studies offer a possible explanation of this inconsistency. In sheep, the placenta enlarges in response to moderate undernutrition in mid pregnancy, presumably reflecting an adaptive response to extract more nutrients from the mother (Robinson et al. 1994); however, this effect is only seen in ewes that were well nourished before conception, and in ewes poorly nourished before conception undernutrition in mid pregnancy is associated with small placental size (Robinson et al. 1994).

**Infant and childhood growth and coronary heart disease**

Evidence suggesting both additive and interactive effects of poor prenatal and infant growth on the risk of subsequent coronary heart disease is now emerging from epidemiological studies. Follow-up of men born in Hertfordshire, UK, between 1911 and 1930 found that lower weight at age 1 year was strongly associated with higher hazard ratios for coronary heart disease (Osmond et al. 1993; Fig. 2.2), and subsequent analyses of this cohort have suggested additive effects of poor fetal and infant growth (Barker 1998).

Confirmation that smaller and thinner infants at age one year have increased rates of coronary heart disease in adulthood has come from people born in the 1930s and 1940s in Helsinki, Finland (Eriksson et al. 2001; Fig. 2.2). These findings, described in detail in Chapter 15, point to the possibility that interactions between the pre- and postnatal environments have an important influence of the risk of coronary heart disease. In the Helsinki study, hazard ratios for coronary heart disease fell with increasing birthweight and, more strongly, with increasing ponderal index at birth. These trends were found in babies born at term or prematurely and therefore reflect slow intrauterine growth. Consistent with the findings in Hertfordshire and with the known association between coronary heart disease and short adult stature (Marmot et al. 1984), men in Helsinki who developed the disease also tended to have poor
weight gain and low rates of height growth in infancy (Chapter 15). Although infant growth failure was deleterious in individuals that were both small and large at birth, childhood weight gain had very different effects in small and large neonates; in relation to the risk of adult coronary heart disease, there was a strong interaction between ponderal index at birth and body mass index in childhood. Among boys who were thin at birth with a below-average ponderal index, rapid weight gain and increasing body mass index during childhood was associated with higher rates of adult coronary heart disease; however, in boys who had an above-average ponderal index at birth, rapid childhood weight gain and increasing body mass index was unrelated to the risk of coronary heart disease (Eriksson et al. 2001). Findings among girls were similar, and again the risk of coronary heart disease was determined more by the tempo of weight gain than the body size attained (Forsen et al. 1999).

**Size of effects and potential confounding influences**

The findings described above suggest that influences linked to pre- and postnatal growth have an important effect on the risk of coronary heart disease. Assessment of the relative importance of early and later-life exposures is difficult as there is a paucity of well-characterised cohorts with both perinatal data and health outcomes documented well into later life. Some commentators have argued that the magnitude of developmental effects on adult cardiovascular risk is small (Hattersley and Tooke 1999, Huxley et al. 2002), although the only published estimate based upon the Helsinki cohort suggests that it is considerable when clinical disease is used as the outcome measure (Barker et al. 2002). Analysis of the magnitude of developmental effects on health 50 or more years later in life is challenging because
concurrent risk factors can often be measured with greater precision and it is difficult to identify or attribute risk to distant, early-life factors. Moreover, the observed relationship between disease risk and birth size does not imply a causal role of being born small but reflects the sensitivity of fetal growth to adverse intrauterine influences. It is thought that it is the effect of environmental influences acting during early development that is the causal trigger. Indeed, much experimental and epidemiological evidence indicates that adverse developmental influences can affect disease risk without birth size being affected.

It has been argued that the associations between size at birth and later disease could primarily reflect genetic influences (Hattersley and Tooke 1999). Recent findings, however, indicate that it is interactions between the early-life environment and genetic influences that are likely to be the principal determinants of disease susceptibility (Eriksson et al. 2002; Chapter 15). Moreover, it is important to recognise that birth size has only a modest genetic component and primarily reflects the quality of the intrauterine environment (Morton 1955, Snow 1989, Brooks et al. 1995).

Other commentators have argued that people whose growth was impaired in utero 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 developmental influences. There is strong evidence that this argument cannot be sustained. In four of the studies which have replicated the association between birthweight and coronary heart disease, data on adult lifestyle factors including smoking, employment, diet, alcohol consumption and exercise were collected (Frankel et al. 1996, Rich-Edwards et al. 1997, Leon et al. 1997, Barker et al. 2001). Allowance for them had little effect on the association between birthweight and coronary heart disease. Influences in adult life, however, add to the effects of the intrauterine environment. For example, the prevalence of coronary heart disease is highest in people who had low birthweight but were obese as adults.

In studies exploring the mechanisms underlying the associations between early growth and later coronary heart disease, there are similar trends between birthweight and major risk factors for cardiovascular disease, including hypertension and type 2 diabetes (Hales et al. 1991, Huxley et al. 2000). Studies of cardiovascular risk factors have been extended to children, and suggest that developmental influences on cardiovascular risk are still acting in today’s children and not simply of historical importance (Hofman et al. 1997, Leeson et al. 1997). These prospective clinical studies of children have again shown that the associations with smaller size at birth are independent of social class, cigarette smoking and alcohol consumption.

A further aspect, suggested by data from the Helsinki cohort, is that the early life and adult environments may not simply have additive effects, but may interact to influence the risk of coronary heart disease. Poverty and low household income have long been linked with coronary heart disease, but recent analyses suggest that this effect occurs in those who are thinner than average at birth, but not in those who are fatter than average (Barker et al. 2001). If interactions between the early-life and adult environments are confirmed, this will have important implications for our understanding of the evolutionary implications of developmental responses (see Chapter 3).

**Stroke, hypertension and cardiovascular function**

As compared with coronary heart disease, epidemiological studies of developmental influences on the risk of stroke have been hampered by the lower population prevalence of the disorder and the paucity of cohorts including both early-life data and information distinguishing occlusive and haemorrhagic stroke. The information that is available suggests that stroke is associated with low birthweight, but not with stunting or thinness (Martyn et al. 1996a). In the Helsinki cohort, the association between small size at birth and haemorrhagic stroke was only significant after adjustment for head circumference, and there was no association with occlusive stroke.
(Eriksson et al. 2000a). Subsequent analyses in a larger Swedish cohort again found that impaired fetal growth was associated with haemorrhagic stroke, but not with occlusive stroke (Hypponen et al. 2001). In the Swedish cohort, the pronounced inverse association between birthweight and haemorrhagic stroke did not depend on adjustment for other birth dimensions, although adjustments for birth length and head circumference strengthened the association with birthweight. The strength of the association between impaired fetal growth and haemorrhagic stroke was appreciably greater than that found with coronary heart disease in the same cohort (Leon et al. 1998).

Hypertension is an important risk factor for both occlusive and haemorrhagic stroke, but there are established differences in the aetiological mechanisms underlying the two subtypes. One such mechanism is carotid atherosclerosis, which is associated with occlusive stroke. There is, however, some evidence linking low birthweight with carotid atherosclerosis. In a group of people aged 70 years, the prevalence and severity of carotid atherosclerosis was greatest in those with the lowest birthweights; when compared with people who weighed over 7.5 pounds (3.4 kg) at birth, the odds ratio of carotid stenosis was 5.3 in those who had weighed 6.5 pounds (2.9 kg) or less at birth (Martyn et al. 1998). Ultrasound measurement of intimal–medial thickness provides an indication of preclinical carotid atherosclerosis; among a group of men and women aged 27–30 years, intimal–medial thickness was increased in those who had experienced severe intrauterine growth restriction, particularly if they also had exaggerated postnatal growth (Oren et al. 2004).

**Hypertension and blood pressure**

Associations between low birthweight and raised blood pressure in childhood and adult life have been extensively demonstrated around the world. A systematic review of published papers described the associations between birthweight and blood pressure (Huxley et al. 2000) in 80 studies of people of all ages in many countries. These associations were not confounded by socioeconomic conditions at the time of birth or in adult life. The difference in systolic pressure associated with a 1-kg difference in birthweight was around 2.0 mm Hg. In clinical practice this would be a small difference but these are large differences between the mean values of populations and may correspond to a substantial proportion of total attributable mortality. Some observers have disputed the relevance of birthweight to blood pressure levels in later life (Huxley et al. 2002), but others have since cautioned about the dangers of extrapolating from a surrogate measure of disease risk, such as blood pressure, to clinical disorders (Gluckman and Hanson 2004). Where clinical disease has been used as the outcome measure, the effect of early environmental influences is clear. Among 22 846 men in the Health Professionals Follow-up Study there were strong relationships between birth size and the risk of developing clinically significant hypertension or diabetes mellitus, but no relationship with systolic blood pressure (Curhan et al. 1996). The findings demonstrate the importance of studying outcomes rather than surrogate measures of disease.

The association between low birthweight and raised blood pressure depends primarily on babies who were born small for dates, after reduced fetal growth, rather than on babies born preterm (Law et al. 1991, Barker et al. 1992, Moore et al. 1999, Eriksson et al. 2000b). In these studies alcohol consumption and higher body mass were also associated with raised blood pressure, but the associations between birthweight and blood pressure were independent of them. Nevertheless body mass remains an important influence on blood pressure and, in humans and animals, the highest pressures are found in those who were small at birth but become overweight as adults (Eriksson et al. 2000b). In some studies the blood pressures of the mothers during and after pregnancy have been recorded. They correlate with the offspring’s blood pressure. However, the associations between body size and proportions at birth and later blood pressure are independent of the mothers’ blood pressures (Law et al. 1991, Martyn et al. 1995a, Barker 1998).
As discussed previously, birthweight is a crude measure of fetal growth that does not distinguish thinness or short length, differences in head size, or variations in the balance of fetal and placental size.Analyses of babies born in Preston, UK, defined two groups who developed raised adult blood pressures (Barker et al. 1992). The first group had below-average placental weight and were thin with a low ponderal index and a below-average head circumference. The second had above-average placental weight and a short crown–heel length in relation to their head circumference; such short babies tend to be fat and may have above-average birthweight. In contrast to the associations between birth size and coronary heart disease, those between birthweight and blood pressure are generally as strong as those between thinness, shortness and blood pressure. Associations between blood pressure and thinness and shortness have been found in some studies but not in others (Barker 1998). In a longitudinal study of young people in Adelaide, Australia, associations between blood pressure and thinness and shortness were not apparent at age 8 years but emerged at age 20 (Moore et al. 1999).

Figure 2.3 shows the systolic pressure of a group of men and women who were born at term in Preston 50 years ago (Barker et al. 1992). Subjects are grouped according to their birthweights and placental weights. As in other studies, systolic pressure falls between subjects with low and high birthweight. In addition, however, there is an increase in blood pressure with increasing placental weight. Subjects with a mean systolic pressure of 150 mm Hg or more, a level sometimes used to define hypertension in clinical practice, comprise a group who as babies were relatively small in relation to the size of their placentas. There are similar trends with diastolic pressure.

A rise in blood pressure with increasing placental weight and a higher ratio of placental weight to birthweight was also found in 4-year-old children in Salisbury, UK, and among young adults in Adelaide, Australia (Law et al. 1991, Moore et al. 1999). In studies of children and adults the association between placental enlargement and raised blood pressure has, however, been inconsistent. As discussed in relation to coronary heart disease, variations in maternal nutritional status prior to conception may underlie some of the inconsistent relations.
with placental weight. For example, three studies that have reported an association between small placental size and raised blood pressure have been in populations in which the mother’s nutritional status was poor or food intake was restricted (Campbell et al. 1996, Eriksson et al. 2000b, Thame et al. 2000).

Mechanisms underlying developmental effects on hypertension and raised blood pressure

There are a number of possible mechanisms by which restricted intrauterine growth could either initiate raised blood pressure or lead to accentuated amplification of blood pressure in later life. Studies in the USA, the UK and Holland have shown that blood pressure in childhood predicts the likelihood of developing hypertension in adult life. These predictions are strongest after adolescence. In children the rise of blood pressure with age is closely related to growth and is accelerated by the adolescent growth spurt. These observations led Lever and Harrap (1992) to propose that essential hypertension is a disorder of growth. The hypothesis that hypertension is a disorder of accelerated childhood growth can be reconciled with the association with low birth-weight by postulating that rapid postnatal compensatory growth plays an important role in amplifying changes established in utero.

Much attention has focused on the possible role of impaired renal development in mediating early-life effects on later hypertension. If the materno-placental supply of nutrients does not match fetal requirements in the last trimester of pregnancy the fetus diverts blood and nutrients to maintain brain metabolism at the expense of the trunk and limbs. This adaptation reduces blood flow to the fetal kidneys and may underlie activation of the fetal renin–angiotensin system in intrauterine growth retardation. A follow-up study of men and women born in Sheffield found, however, that those who had been small at birth had lower plasma concentrations of inactive and active rennin (Martyn et al. 1996b). Causes of raised blood pressure that are not mediated by increased renin release tend to result in low concentrations of renin. These findings therefore suggest that the association between impaired fetal growth and raised blood pressure involves mechanisms other than the renin–angiotensin system. Low concentrations of renin in adult life do not, however, exclude the possibility of an earlier but lasting influence of the renin–angiotensin system, and the possible consequences of early activation of the system are discussed further in Chapter 23.

An alternative explanation for the low plasma renin concentrations of people who were small at birth is that they reflect a relative deficit of nephrons. Brenner suggested that retarded fetal growth leads to reduced numbers of nephrons, increasing pressure in the glomerular capillaries and glomerular sclerosis (Mackenzie and Brenner 1995). This sclerosis results in further loss of nephrons and a self-perpetuating cycle of hypertension and progressive glomerular injury. The numbers of nephrons is established during fetal life and varies widely in the normal population, with a normal range of around 300 000 to 1 100 000 or more (Mackenzie and Brenner 1995). Studies using fetal ultrasound have shown that babies that are small for gestational age have reduced renal growth during a critical period between 26 and 34 weeks of gestation. This reduces the antero-posterior size of the kidney but does not diminish kidney length (Konje et al. 1996). Direct support for the hypothesis that the number of nephrons plays an important role in primary hypertension has come from a case-control study of the number of glomeruli in 10 patients with primary hypertension and 10 matched normotensive subjects, all of whom had died in accidents. The median number of glomeruli per kidney was 702 379 in the hypertensive patients and 1 429 200 in the normotensive controls (Keller et al. 2003). Chapter 23 describes animal studies which provide substantial experimental evidence supporting the importance of impaired intrauterine renal development.

Animal studies also provide much evidence that re-setting of homeostatic neuroendocrine mechanisms controlling blood pressure is likely to be involved in mediating developmental effects on later blood pressure. A number of the maternal exposures that impair fetal growth are associated with
alterations in the fetus’s hypothalamic–pituitary–adrenal axis, and Chapter 13 describes evidence that this can alter the set-point of the biological response to stress. Altered sympathoadrenal and hypothalamic–pituitary–adrenal responses to stress are likely to be important mechanisms by which adverse influences during development affect the health of the offspring, and it is now known that people who had low birthweight have increased stress sensitivity, as indicated by cardiovascular responses, hypothalamic–pituitary–adrenal axis activity and sympathoadrenal responses. A review concluded that smaller birth size is associated with higher adult fasting plasma cortisol concentrations (Phillips et al. 2000); more detailed studies of the hypothalamic–pituitary–adrenal axis are required to define the underlying mechanism. People with high blood pressure tend to have features of increased sympathetic nervous system activity, including a high resting pulse rate, a high cardiac output and a hyperdynamic circulation. Among men and women in Preston, those who had low birthweight had a higher resting pulse rate (Phillips and Barker 1997). This is consistent with the hypothesis that retarded growth in utero establishes increased sympathetic nervous activity and contributes to raised blood pressure in later life.

**Cardiovascular structure and function**

Evidence that developmental influences can have long-term effects on cardiac structure came initially from a follow up study of 290 men born during 1920–30. Using echocardiography it was found that left ventricular mass increased with lower weight at age one-year, but was not related to birthweight (Vijayakumar et al. 1995). The relation with weight at 1 year was independent of adult body size, systolic blood pressure and age, leading to speculation that the left ventricular enlargement may be a long-term result of haemodynamic changes in utero or of persisting changes in growth factor concentrations. Subsequently, echocardiography of 210 children and young adults found a concentric increase in left ventricular mass, adjusted for sex and current body size, with decreasing weight at 9 months or 2 years, even though there was no association between systolic pressure and weight at these ages (Zureik et al. 1996). Support for the hypothesis that left ventricular mass might be partly determined during fetal life and early infancy has come from experiments in pregnant guinea pigs and sheep; maternal food restriction in early pregnancy resulted in increased left ventricular mass in the postnatal offspring (Khan et al. 2005). Mechanisms underlying developmental effects on cardiac structure are discussed in Chapter 20.

The content and arrangement of elastin in the aorta and large conduit arteries plays an important part in minimising the rise of blood pressure in systole and maintaining blood pressure in diastole. Elastin is only synthesised in early life and the gradual loss or fracture of elastin fibres is thought to contribute to the rise in systolic and pulse pressure with ageing. These considerations have led to the hypothesis that impaired fetal development may be associated with a relative deficiency in elastin synthesis, resulting in stiffer arteries and raised blood pressure in postnatal life (Martyn and Greenwald 1997). This hypothesis is supported by a study of 50-year-old men and women showing that those who had a small abdominal circumference at birth tended to have a higher pulse wave velocity and decreased arterial elasticity in adult life (Martyn et al. 1995a).

Recent studies suggest that, in addition to its associations with compliance, low birthweight is also associated with persisting alterations in vascular structure and function. Hertfordshire men who had had low birthweight had narrow bifurcation angles in their retinal blood vessels (Chapman et al. 1997). People with hypertension have similar changes in retinal vascular geometry.

In the search for mechanisms which link reduced early growth with cardiovascular disease, evidence has emerged suggesting that functional abnormalities of the vasculature may be important. Vascular endothelial dysfunction is a key early event in atherosclerosis and is important in the development of the diseases associated with poor early growth. It is seen in subjects with coronary artery disease...
and type 2 diabetes and is closely associated with insulin resistance. Several studies have suggested that there is a relationship between birthweight and endothelial dysfunction that is present in children as early as the first decade of life. This was first reported in a study of 333 British children aged 9–11 years, which showed that the ability of the brachial artery to dilate in response to increased blood flow (induced by forearm cuff occlusion and release), an endothelium-dependent response, was reduced in children who had been small at birth (Leeson et al. 1997). It was confirmed in a study of 9-year-old children in Sweden (Martin et al. 2000). Other studies showed that this association persists into adult life, including a UK case–control study of 19 to 20-year-old subjects of low compared with normal birthweight (Goodfellow et al. 1998). The adult studies suggest that birthweight has a substantial effect similar in magnitude to the effect of smoking. Chapter 21 discusses the mechanisms underlying a developmental influence on endothelial function.

Serum cholesterol and blood clotting

Studies in Sheffield, UK, show that the neonate that has a short body and low birthweight in relation to the size of its head has persisting disturbances of cholesterol metabolism and blood coagulation (Barker 1998). Disproportion in body length relative to head size is associated with redistribution of blood flow away from the trunk to sustain the brain. This affects blood flow to the liver, two of whose functions, regulation of cholesterol and of blood clotting, seem to be permanently perturbed. Disturbance of cholesterol metabolism and blood clotting are both important features predisposing to cardiovascular disease.

The Sheffield records included abdominal circumference at birth, as well as length, and it was specifically reduction in this birth measurement that predicted raised serum concentrations of total and low-density-lipoprotein cholesterol and apolipoprotein B in men and women (Barker et al. 1993b). The differences in concentrations across the range of abdominal circumference were large, statistically equivalent to 30 per cent differences in mortality from coronary heart disease. Findings for plasma fibrinogen concentrations, a measure of blood coagulability, were of similar size (Martyn et al. 1995b). Small abdominal circumference at birth also predicted death from coronary heart disease (Barker et al. 1995). Abdominal circumference in a neonate indicates liver size as well as the fatness of the abdominal wall, and one interpretation is that impaired liver growth is associated with persisting changes in liver metabolism. The Sheffield findings suggest that birthweight is a poor surrogate for developmental influences on liver metabolism and that caution should be exercised when making inferences from studies lacking more detailed information on prenatal growth and development (Huxley et al. 2004).

Animal experiments provide strong support for both pre- and postnatal influences on the ‘setting’ of lipid metabolism, as described in Chapter 11. The findings relating to postnatal influences on human lipid metabolism are less consistent. However, evidence from follow-up of men and women born in Hertfordshire, UK, suggests that poor infant growth, exclusive bottle-feeding and breast-feeding beyond 1 year may be associated with raised serum concentrations of total and low-density-lipoprotein cholesterol and apolipoprotein B (Fall et al. 1992).

Type 2 diabetes and the metabolic syndrome

Insulin has a central role in fetal growth, and disorders of glucose and insulin metabolism are therefore an obvious possible link between early growth and cardiovascular disease. Although obesity and a sedentary lifestyle are known to be important in the development of type 2 diabetes, they seem to lead to the disease only in predisposed individuals. Family and twin studies have suggested that the predisposition is familial, but the nature of this predisposition is unknown. The disease tends to be transmitted through the maternal rather than paternal side of the family.
Size at birth and type 2 diabetes

A number of studies have confirmed the association between birthweight and impaired glucose tolerance and type 2 diabetes first reported in Hertfordshire (Hales et al. 1991, McCance et al. 1994, Curhan et al. 1996, Lithell et al. 1996). In the Health Professionals Study, USA, the odds ratio for diabetes, after adjusting for current body mass, was 1.9 among men whose birthweights were less than 5.5 pounds (2.5 kg) compared with those who weighed 7.0 to 8.5 pounds (3.2–3.9 kg) (Curhan et al. 1996). Among the Pima Indians, USA, the odds ratio for diabetes was 3.8 in men and women who weighed less than 5.5 pounds (McCance et al. 1994). In Preston it was the thin babies who developed impaired glucose tolerance and diabetes (Phillips et al. 1994a). Lithell and colleagues (1996) confirmed the association with thinness in Uppsala, Sweden: the prevalence of diabetes was three times higher among men in the lowest fifth of ponderal index at birth. Among the Pima Indians diabetes in pregnancy is unusually common and the association between birthweight and type 2 diabetes is U-shaped, with an increased prevalence in young people with birthweights over 9.9 pounds (4.5 kg) (McCance et al. 1994). The increased risk of diabetes among those of high birthweight was associated with maternal diabetes in pregnancy.

Both deficiency in insulin production and insulin resistance are thought to be important in the pathogenesis of type 2 diabetes. There is evidence that both may be determined in fetal life. As discussed further in Chapter 16, infants who are small for dates have fewer pancreatic β cells and there is evidence that nutritional and other factors determining fetal and infant growth influence the size and function of the adult β cell complement (Hales and Barker 1992). Whether and when type 2 diabetes supervenes will be determined by the rate of attrition of β cells with ageing, and by the development of insulin resistance, of which obesity is an important deterrent.

While some studies of adults have found no association between birthweight and insulin responses to infused glucose (Alvarsson et al. 1994), it is possible that insulin resistance in adult life changes insulin secretion and obscures associations with fetal growth. Studies of younger people may resolve this. A study of men aged 21 years showed that those with lower birthweight had reduced plasma insulin concentrations 30 minutes after a glucose challenge (Robinson et al., 1992). Another study of men of similar age showed that a low insulin response to glucose was associated with high placental weight and a high ratio of placental weight to birthweight (Wills et al. 1996). In contrast, a study of young Pima Indians showed that those with low birthweight had evidence of insulin resistance but no defect in insulin secretion (Leger et al. 1997a).

In Mysore, south India, men and women with type 2 diabetes showed signs of both insulin resistance and deficiency (Fall et al. 1998). As in people from south India living in Britain, there was a high prevalence of insulin resistance and central adiposity in this population. Those in Mysore who had type 2 diabetes, however, also had a low insulin increment after a glucose challenge, indicating insulin deficiency as well as resistance. Whereas, however, insulin resistance was associated with low birthweight, type 2 diabetes was associated with shortness at birth in relation to birthweight, that is a high ponderal index, and with maternal adiposity (Fall et al. 1998). As set out in Chapter 35, these findings led to a novel hypothesis to account for the epidemic of type 2 diabetes in urban and migrant Indian populations (Fall et al., 1998).

Insulin resistance and the metabolic syndrome

Men and women with low birthweight have a high prevalence of the ‘insulin resistance syndrome’ or ‘metabolic syndrome’ (Barker et al. 1993c), in which impaired glucose tolerance, hypertension and raised serum triglyceride concentrations occur in the same patient. Phillips et al. (1994b) carried out insulin tolerance tests on 103 men and women in Preston, UK. At each body mass, insulin resistance was greater in people who had a low ponderal index at birth. Conversely, at each ponderal index, resistance was greater in those with high body mass. The greatest insulin resistance was therefore in those with
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low ponderal index at birth but high current body mass.

A study in San Antonio, Texas, confirmed the association between low birthweight and the insulin resistance syndrome in 30-year-old Mexican-Americans and non-Hispanic white people (Valdez et al. 1994). Among men and women in the lowest third of the birthweight distribution and the highest third of current body mass 25% had the syndrome. By contrast, none of those in the highest third of birthweight and lowest third of current body mass had it. A study of young adults in France showed that those who had had intrauterine growth retardation had raised plasma insulin concentrations when fasting and after a glucose challenge (Leger et al. 1997b). They did not show any of the other abnormalities that occur in the insulin resistance syndrome. This suggests that insulin resistance may be a primary abnormality to which other changes are secondary. Follow-up of men and women who were in utero during the Dutch famine provides evidence that maternal undernutrition can programme insulin resistance and type 2 diabetes (Ravelli et al. 1998). Those exposed to famine in utero had higher two-hour plasma glucose and insulin concentrations than those born before or conceived after the famine.

Law et al. (1995) reported associations between thinness at birth and raised 30-minute plasma glucose concentrations in 7-year-old children in Salisbury, UK. In a group of older children, Whincup (1997) found that those who had lower birthweight had raised plasma insulin concentrations, both fasting and after oral glucose, suggesting insulin resistance. Among these children, however, those who had low birthweight had normal plasma glucose concentrations, which implies that despite being insulin resistant they were currently able to maintain glucose homeostasis. More recently, follow-up of children who were born prematurely has shown that they have an isolated reduction in insulin sensitivity as compared with controls (Hofman et al. 2004). These and other findings in children support an intrauterine origin for type 2 diabetes and suggest that the seeds of diabetes in the next generation have already been sown and are apparent in today’s children (Chapter 14).

The processes that link thinness at birth with insulin resistance in adult life are not known, but experimental studies are now providing important clues (Chapter 17). Babies born at term with a low ponderal index have a reduced mid-arm circumference and low muscle bulk. It is possible that thinness at birth is associated with abnormalities in muscle structure and function that originate in mid gestation and have long term consequences that interfere with insulin’s ability to promote glucose uptake in skeletal muscle. Magnetic resonance spectroscopy studies show that people who were thin at birth have lower rates of glycolysis and glycolytic ATP production during exercise (Taylor et al. 1995). More recently, magnetic resonance studies have investigated skeletal muscle metabolism in the healthy offspring of patients with type 2 diabetes; insulin resistance in the offspring was associated with dysregulation of intramyocellular fatty acid metabolism (Petersen et al. 2004). An inherited defect in mitochondrial oxidative phosphorylation is one explanation, but an intrauterine effect transmitted across generations is an alternative possibility. In response to undernutrition a fetus may reduce its metabolic dependence on glucose and increase oxidation of other substrates, including amino acids and lactate. This raises the possibility that a glucose-sparing metabolism persists into adult life, and that insulin resistance arises as a consequence of similar processes, possibly because of reduced rates of glucose oxidation in insulin-sensitive peripheral tissues.

When the availability of nutrients to the fetus is restricted, concentrations of anabolic hormones, including insulin and insulin-like growth factor 1, fall, while catabolic hormones, including glucocorticoids, rise. As discussed in Chapter 19, persisting hormonal changes could contribute to the development of the metabolic syndrome. Bjorntorp (1995) has postulated that glucocorticoids, growth hormone and sex steroids may play major roles in the evolution of the metabolic syndrome.
Table 2.1 Body mass index at 1 and 12 years and cumulative incidence of type 2 diabetes according to age at adiposity rebound. Data from Eriksson et al. (2003).

<table>
<thead>
<tr>
<th>Age at adiposity rebound (yrs)</th>
<th>BMI at 1 year (kg m$^{-2}$)</th>
<th>BMI at 12 years</th>
<th>Cumulative incidence of diabetes %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4</td>
<td>16.9</td>
<td>20.1</td>
<td>8.6</td>
</tr>
<tr>
<td>5</td>
<td>16.9</td>
<td>17.9</td>
<td>4.4</td>
</tr>
<tr>
<td>6</td>
<td>17.7</td>
<td>17.2</td>
<td>3.2</td>
</tr>
<tr>
<td>7</td>
<td>18.2</td>
<td>17.1</td>
<td>2.2</td>
</tr>
<tr>
<td>≥8</td>
<td>18.4</td>
<td>16.9</td>
<td>1.8</td>
</tr>
<tr>
<td>p for trend</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Obesity and the adiposity rebound

The studies described earlier found that people who were small at birth and had low infant weight gain are at particular risk of adult coronary heart disease if they become overweight in childhood. After age 2 years the body mass index of normal young children falls to a minimum around 6 years before rising again, the so-called adiposity rebound (Rolland-Cachera et al. 1987). Early age at adiposity rebound has been related to obesity in childhood and adult life (Whitaker et al. 1997).

Data from Helsinki showed for the first time that early age at adiposity rebound is a strong predictor of type 2 diabetes (Eriksson et al. 2003); this observation has since been replicated in Delhi, India (Bhargava et al. 2004). Table 2.1 shows this trend is remarkably strong, even without taking adult obesity into account. Overall, the Helsinki observations showed that slow growth in utero, low weight gain in infancy and early age at adiposity rebound in later childhood are associated with large increases in the incidence of type 2 diabetes. The adiposity rebound may primarily reflect crossing of BMI centiles, but most cohort studies have lacked the detailed longitudinal pre- and postnatal anthropometric data to fully characterise the adiposity rebound and its causes; surprisingly, thinness at age 1 year was a strong predictor in the Helsinki data (Table 2.1). The importance of collecting detailed body-composition measurements in well-characterised children is emphasised by data from the US National Collaborative Perinatal Project showing that greater weight gain from birth to age 4 months is also a major risk factor for later obesity (Stettler et al. 2003).

Musculoskeletal health

Osteoporosis is a common skeletal disorder in developed communities characterised by low bone mass and microarchitectural deterioration of bone tissue predisposing to fracture. The disorder has major health implications; among European people aged 50 years or older the lifetime risk of fracture at the hip, spine and wrist is 39% in women and 13% in men. Much recent evidence has shown that the risk of osteoporotic fracture is modified by environmental influences during intrauterine and early postnatal life (Harvey and Cooper 2004). Studies in the US, UK, Sweden and Australia have shown that low birthweight and weight at one year are associated with low bone mass in adult life, as assessed by dual energy X-ray absorptiometry (Cooper et al. 1997, Yarbrough et al. 2000, Javaid and Cooper 2002). The relationships are independent of known environmental risk factors for osteoporosis including smoking, alcohol consumption, lack of exercise and low calcium intakes. Longitudinal studies in Finland have shown that low birthweight and slow postnatal skeletal growth are associated with higher rates of hip fracture (Cooper et al. 2001).

Preliminary data suggest important interactions between birthweight and genes that predict adult bone mass, including the vitamin D receptor gene (Dennison et al. 2001). Follow-up of children to age 9 years has demonstrated that a low ionised calcium concentration in cord blood is associated with reduced childhood bone mass, and that both measurements correlate with reduced circulating maternal 25(OH) vitamin D levels (Javaid et al. 2003). Maternal vitamin D insufficiency may therefore lead to retarded intrauterine and postnatal skeletal development, with a consequent reduction in peak bone mass and elevated risk of fracture in late adulthood. Other maternal characteristics are
now known to influence the bone mineral content of babies. Maternal smoking, low maternal fat stores and high maternal physical activity in late gestation are independently associated with reduced neonatal bone mineral content (Godfrey et al. 2001).

Developmental influences on skeletal muscle mass and function may contribute to the increased fracture risk in individuals whose early growth was restricted (Syddall et al. 2003, Sayer et al. 2004). Muscle strength also has a major impact on the age-related decline in physical performance, quality of life and mortality. Lower birthweight has been linked with lower adult muscle mass (Phillips 1995, Gale et al. 2001), altered muscle metabolism (Phillips et al. 1994c) and reduced muscle strength (Sayer et al. 1998). Follow-up of men and women aged 53 years in the Medical Research Council National Survey of Health and Development found that lower birthweight was associated with reduced adult grip strength, even after adjustment for height and weight in both childhood and adult life (Kuh et al. 2002). The mechanisms through which the early-life environment may influence musculoskeletal health in adult life are discussed further in Chapter 29.

Respiratory health and atopy

Chronic obstructive airways disease was one of the original disorders for which ecological studies suggested an important developmental influence (Barker 1998), but subsequent epidemiological studies have tended to neglect investigation of developmental influences on respiratory health and atopy. Several studies have suggested that maternal smoking before and after birth may be associated with impaired lung function of the offspring, but not all studies have found such as effect (Hanrahan et al. 1992, Murray et al. 2002, Stocks and Dezateux 2003). Independently of maternal smoking, children and adults who were small at birth tend to have reduced lung function (Barker et al. 1991, Rona et al. 1993, Stein et al. 1997, Nikolajev et al. 1998) and an increased risk of respiratory morbidity and mortality (Barker et al. 1991, Svanes et al. 1998). The normal physiological growth and development patterns of the airways and parenchyma remain poorly understood, but epidemiological studies measuring premorbid lung function in infancy indicate the importance of genetic and environmental factors during fetal and early postnatal life (Clarke et al. 1995, Stick et al. 1996, Dezateux et al. 1999). In 131 normal infants aged 5–14 weeks, we recently found that smaller birth size and higher early-infancy weight gain were associated with lower forced expiratory volume at 0.4 s and lower forced expiratory flow at functional residual capacity (Lucas et al. 2004): these suggest impaired lung development and may predispose to obstructive airways disease, including asthma.

Although the mechanisms linking early lung development with lung function in later life are unknown, impaired airway and alveolar growth may be important. Airway branching is complete by 16 weeks gestation, and alveolar formation begins before birth. Between birth and 18 months of age there is a rapid increase in alveolar number and size, whilst airway diameter continues to grow. Environmental influences during both prenatal and early postnatal life therefore have the potential to affect lung development. These are discussed further in Chapter 25.

Fetal and postnatal growth have been associated with later atopy and asthma, and Chapter 26 describes evidence that early-life exposure to infections and pollutants may have long-term effects on immune function and atopy. Links between a large neonatal head circumference and a raised total serum IgE in childhood (Gregory et al. 1999, Leadbitter et al. 1999) and adulthood (Godfrey et al. 1994a) led to the hypothesis that factors influencing fetal growth may programme the developing immune system (Beasley et al. 1999). Birth length and weight have been associated with later asthma (Leadbitter et al. 1999), but this was not replicated in another study (Svanes et al. 1998). The conflicting results may reflect the age at which the relationship is examined, and whether persistent wheezing associated with atopy is considered separately from transient wheezing in children with small airways.
who are predisposed to wheeze with viral infections (Martinez et al. 1995).

**Cognitive function and mental health**

**Brain growth and cognitive function in childhood and old age**

There is evidence that elderly adults with larger head sizes not only tend to gain higher scores on tests of IQ and memory function, but are also less likely to show a decline in these scores over time (Gale et al. 2003) and less likely to develop Alzheimer’s disease in later life (Schofield et al. 1997). Because head size is known to correlate closely with brain volume, these findings suggest that brain development in the first few years of life is important in determining how well cognitive abilities are preserved in old age. Developmental influences on ageing are discussed further in Chapter 32. Studies in children have shown the importance of brain growth in the early years after birth for the attainment of high levels of cognition. At 9 years, IQ scores were highest in those who had experienced a large increase in head circumference between birth and 9 months of age and a further large increase in head circumference between 9 months and 9 years of age (Gale et al. 2004). These associations persisted after controlling for maternal factors, including the mother’s IQ, education and social class.

**Schizophrenia and mood disorders**

It has long been hypothesised that perinatal influences play an important role in the genesis of major brain disorders (Pasamanick et al. 1956). Advances in neuropathology and imaging have led to the conclusion that schizophrenia may indeed have a developmental basis (Pilowsky et al. 1993), perhaps originating through abnormal neuronal migration (Akbarian et al. 1996). This conclusion is supported by evidence that intrauterine exposures and obstetric complications are associated in later life with the brain dysfunction that characterises the disorder (Brixey et al. 1993, Cannon et al. 2002). Maternal influenza infection in mid trimester has been linked with an increased risk of schizophrenia in the offspring (Mednick et al. 1988), although other studies of maternal influenza have provided inconsistent findings (Weinberger 1995). Evidence for a role of maternal nutrition has come from follow-up studies of the offspring of women who were pregnant during the Dutch famine: famine exposure during the first trimester was found to double the risk of schizophrenia in adult life (Susser et al. 1996, Hoek et al. 1998).

Epidemiological studies of the Dutch famine suggest that intrauterine influences may also increase the risk of affective disorders and low mood in the offspring (Brown et al. 1995). Although adverse life events are often the proximal cause of depressive illness, these act selectively on vulnerable individuals, and it has been proposed that both genetic and intrauterine influences may determine this vulnerability (Thompson et al. 2001). Evidence for an effect of the intrauterine environment in determining the later risk of mental illness has come from observations in the 1958 British birth cohort study, in which Sacker et al. (1995) found lower birthweight in patients admitted with affective psychosis. Subsequent studies in Sweden (Mittendorfer-Rutz et al. 2004) and Hertfordshire, UK (Thompson et al. 2001) have found that low birthweight increases the risk of suicide and depression in adolescence and adult life. In the Swedish study of 713,370 young adults, restricted fetal growth and teenage motherhood were associated with both suicide completion and attempt in the offspring, influences that acted independently of the mother’s parity and education (Mittendorfer-Rutz et al. 2004). The biological bases for these and other early-life effects on brain function are discussed further in Chapters 27 and 28.

**Maternal influences on development and offspring health**

The demonstration that normal variations in fetal size and proportions at birth have implications for health throughout life has prompted a re-evaluation of maternal influences on fetal growth and development. Much experimental and epidemiological
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Fetal gene expression

Fetal nutrient demand > supply
Fetal endocrine milieu
Placental vascular impedance

Fetal developmental plastic responses
- altered endocrinology/metabolism
- changes in fetal bone, lean & fat mass
- altered blood flow/vascular loading

Modification / amplification in infancy / childhood

Susceptibility to adversity in adulthood

Cardiovascular & metabolic disease

Figure 2.4 A conceptual framework for the developmental-origins hypothesis.

Research now suggests that maternal diet, body composition and other influences can have important long-term effects on the health of the offspring, and that these long-term effects can operate without necessarily affecting usually measured pregnancy outcomes such as birthweight.

Research to date has linked specific maternal influences with the adult health of the offspring, notably: (1) the mother’s own birthweight, (2) maternal body composition, including fat and lean mass, (3) maternal dietary intakes, including macro- and micronutrient balance, (4) maternal endocrine status. There is increasing evidence that fetal development can be affected by nutritional variation within the normal range of western diets, and many women eat unbalanced diets or constrain their weight by dieting (Godfrey 2000). Furthermore, studies of the Dutch famine indicate that the longer-term effects on offspring may depend on the duration and timing of famine exposure and can be independent of birth size (Roseboom et al. 2001a). Although nutrition has received the most focus (Langley and Jackson 1994, Vickers et al. 2000, Bertram and Hanson 2001), other early environmental factors such as infection, season of birth (Doblhammer and Vaupel 2001) and smoking (Power and Jefferis 2002) may also have long-term effects.

We have proposed that the mechanisms through which maternal influences lead to developmental plastic responses include (a) a mismatch between fetal nutrient demands, largely determined by the growth trajectory set in early pregnancy, and the maternoplacental capacity to meet this demand, (b) alterations in the fetal endocrine milieu, and (c) changes in placental vascular impedance, which impact on fetal cardiovascular loading. There is now evidence that the consequences of developmental plastic responses can be modified during infancy, and that their effects can be amplified by high childhood weight gain and perhaps by low levels of habitual physical activity, increasing vulnerability to adverse lifestyle influences during adulthood. This conceptual framework is illustrated in Fig. 2.4.

Periconceptional influences and the early trajectory of fetal growth

Size at birth is the product of the fetus’s trajectory of growth, which is set at an early stage in development, and the maternoplacental capacity to supply sufficient nutrients to maintain that trajectory. In western communities, randomised controlled trials
of maternal macronutrient supplementation have had relatively small effects on birthweight (Chapter 8 and Kramer 1993). This has led to the view that regulatory mechanisms in the maternal and placental systems act to ensure that human fetal growth and development is little influenced by normal variations in maternal nutrient intake, and that there is a simple relationship between a woman’s body composition and the growth of her fetus. Subsequent experimental studies in animals and observational data in humans challenge these concepts. They suggest that a mother’s dietary intakes and body composition around the time of conception and during pregnancy can exert major effects on the balance between the fetal demand for nutrients (Kwong et al. 2000) and the maternoplacental capacity to meet that demand (Duggleby and Jackson 2001).

A rapid trajectory of growth increases the fetus’s demand for nutrients. Though fetal demand for nutrients is greatest late in pregnancy, the magnitude of this demand is thought to be primarily determined by genetic and environmental effects on the trajectory of fetal growth, which is set at an early stage in development. Experimental studies of pregnant ewes have shown that, although a fast growth trajectory is generally associated with larger fetal size and improved neonatal survival, it renders the fetus more vulnerable to a reduced maternoplacental supply of nutrients in late gestation. Thus, maternal undernutrition during the last trimester adversely affects the development of rapidly growing fetuses with high requirements, while having little effect on those growing more slowly (Harding et al. 1992). Rapidly growing fetal lambs were found to make a series of adaptations in order to survive, including fetal wasting and placental oxidation of fetal amino acids to maintain lactate output to the fetus (Barker et al. 1993d).

Experiments in animals have shown that alterations in maternal diet around the time of conception can change the fetal growth trajectory. In a recent study, rats were fed a 9% casein low-protein diet in the periconceptional period. This led to reduced stem cell populations being formed during embryonic development for later fetal and placental lineage pathways, and to small size at birth, compensatory postnatal growth and raised blood pressure in the offspring during adult life (Kwong et al. 2000 and Chapter 4). Early embryos from sheep and cattle are also sensitive to environmental conditions leading to loss of fetal growth control known as ‘large offspring syndrome’ and increased postnatal disease (Walker et al. 2000). The sensitivity of the human embryo to its environment is being increasingly recognised with the development of assisted reproductive technology and the reported low birthweight of singleton IVF babies compared with those from natural conception (Walker et al. 2000, Winston and Hardy 2002). The trajectory of fetal growth is thought to increase with improvements in periconceptional nutrition, and is faster in male fetuses. The consequent greater vulnerability of male fetuses to undernutrition may contribute to the higher death rates from coronary heart disease among men. Characterisation of maternal influences on the early growth trajectory of the human fetus is now an important priority.

**Transgenerational effects**

The supply of nutrients to the human fetus depends on the long and vulnerable series of steps known as the fetal supply line; this includes the mother’s body composition and size, her metabolism, and transport of nutrients to and across the placenta. Part of the fetal supply line is established during the mother’s own intrauterine life. Strong evidence for major intergenerational effects in humans has come from studies showing that a woman’s birthweight influences the birthweight of her offspring (Emanuel et al. 1992). A study in the UK showed that whereas low-birthweight mothers tended to have thin infants with a low ponderal index, the father’s birthweight was unrelated to ponderal index at birth (Godfrey et al. 1997). The effect of maternal birthweight on thinness at birth is consistent with the hypothesis that in low-birthweight mothers the fetal supply line is compromised and unable to meet fetal nutrient demand. These and other observations have
led to the conclusion that mothers constrain fetal growth and that the degree of constraint they exert is set when they are in utero. Potential mechanisms underlying this effect include alterations in the uterine or systemic vasculature, changes in maternal metabolism and impaired placentation.

A study in Preston, UK, showed that young men and women whose mothers had low birthweight have raised blood pressure even after allowing for their mothers’ blood pressure; father’s birthweight was not related to the offspring’s blood pressure (Barker et al. 2000). This led to the conclusion that if the growth of a female fetus is constrained by lack of nutrients there are persisting changes in its physiology and metabolism which lead to reduced fetal nutrition and raised adult blood pressure in the next generation. Little is known about the effects of intergenerational transmission of retarded fetal growth on coronary heart disease, or other degenerative disorders, in the next generation, although it is known that women who had low-birthweight babies have increased rates of cardiovascular disease (Smith et al. 2000).

Experimental studies in animals have shown that undernutrition can have effects on reproductive performance, which may persist for several generations (Drake and Walker 2004). Among rats fed a protein-deficient diet over 12 generations there was a progressive fall in fetal growth rates. When restored to a normal diet it took three generations before growth and development were normalised (Stewart et al. 1980). The existence of strong intergenerational effects on fetal growth is important for public health today. Improvements in women’s diets are likely to benefit more than one generation.

Maternal influences on placental size and transfer capabilities

Little is known about maternal influences on placental function, but there is more evidence in relation to placental growth and structure. This suggests effects of maternal metabolic and endocrine status, of maternal hypoxaemia and anaemia, and of maternal diet and nutritional status, particularly in the periconceptional period (Godfrey 2002).

Although the size of the placenta gives only an indirect measure of its capacity to transfer nutrients to the fetus, it is nonetheless strongly associated with fetal size at birth. Experiments in sheep have shown that maternal undernutrition in early pregnancy can exert major effects on the growth of the placenta, and thereby alter fetal development (Robinson et al. 1994). As previously referred to, the effects produced depend on the nutritional status of the ewe in the periconceptional period. In ewes poorly nourished around the time of conception, high nutrient intakes in early pregnancy increased the size of the placenta. Conversely, in ewes well nourished around conception, high intakes in early pregnancy resulted in smaller placental size (Robinson et al. 1994). Although this suppression of placental growth appears paradoxical, in sheep farming it is common practice for ewes to be put on rich pasture prior to mating and then on poor pasture for a period in early pregnancy. Support for important nutritional effects on placental growth and structure comes from studies in guinea pigs, in which food restriction before and during pregnancy reduced the exchange surface area and increased the arithmetic mean barrier thickness to diffusion (Roberts et al. 2001). In this model, maternal food restriction not only reduced placental weight, but also induced structural alterations that would result in functional impairment beyond that expected for the reduction in weight.

There is evidence that high dietary intakes in early pregnancy can suppress placental growth in humans (Godfrey et al. 1996). Among women who delivered at term in Southampton, UK, those with high dietary intakes in early pregnancy, especially intakes of carbohydrate, had smaller placentas, particularly if this was combined with low intakes of dairy protein in late pregnancy. These effects were independent of the mother’s body size, social class and smoking, and resulted in alterations in the ratio of placental weight to birthweight and in a low ponderal index at birth (Godfrey et al. 1997). Further evidence that maternal diet can alter placental growth has come from the Dutch famine, in which famine exposure in
early pregnancy increased placental weight (Lumey 1998).

The U-shaped relation between the placental ratio and later coronary heart disease found in men born earlier last century in Sheffield (Martyn et al. 1996a) suggests that effects on placental growth could be of long-term importance. Babies with a disproportionately small placenta may suffer as a consequence of an impaired placental supply capacity; those with a disproportionately large placenta may experience fetal catabolism and wasting to supply amino acids for placental consumption (Barker et al. 1993d). Consequent fetal adaptations may underlie the increased adult coronary heart death rates in those with both low and high placental ratios.

Maternal diet and body composition

Direct evidence supporting a long-term effect of levels of maternal nutrient intake during pregnancy has come from a follow-up study of children whose mothers took part in a randomised controlled trial of calcium supplementation in pregnancy in Argentina (Belizan et al. 1997). Supplementation was associated with lowering of the offspring’s blood pressure in childhood. Follow-up studies of people exposed to the Dutch famine of 1944–5 showed that severe maternal caloric restriction at different stages of pregnancy was variously associated with obesity, dyslipidaemia and insulin resistance in the offspring, and there is preliminary evidence of an increased risk of coronary heart disease among people conceived during the famine (Ravelli et al. 1998, Roseboom et al. 2000a, 2000b).

In the Dutch studies, famine exposure per se was not associated with raised blood pressure in the offspring, but there was evidence for an effect of macronutrient balance. Maternal rations with a low protein density were associated with raised blood pressure in the adult offspring (Roseboom et al. 2001b). Similarly, among adolescent boys, systolic blood pressure was inversely related to the mothers’ percentage of dietary energy from protein (Adair et al. 2001). This adds to the findings of studies in Aberdeen, UK, which showed that maternal diets with either a low or a high ratio of animal protein to carbohydrate were associated with raised blood pressure in the offspring during adult life (Campbell et al. 1996). In the Aberdeen study maternal diets with a high protein density were associated not only with raised blood pressure in the offspring but also with insulin deficiency and impaired glucose tolerance (Shiell et al. 2000). While it may seem counterintuitive that a high-protein diet should have adverse effects, these findings are consistent with the results of controlled trials of protein supplementation in pregnancy, which show that high protein intakes are associated with reduced birthweight (Rush 1989).

The Aberdeen findings have recently been replicated in a follow-up study of men and women in Motherwell, UK, whose mothers were advised to eat a high-meat-protein, low-carbohydrate diet during pregnancy (Shiell et al. 2001). Those whose mothers had high intakes of meat and fish in late pregnancy, but low intakes of carbohydrate, had raised blood pressure – particularly if the mother also had a low intake of green vegetables. One possibility is that the effect on blood pressure may be a consequence of the metabolic stress imposed on the mother by an unbalanced diet in which high intakes of essential amino acids are not accompanied by the micronutrients required to utilise them. Evidence in support of this comes from analysis of the offspring’s fasting plasma cortisol concentrations (Herrick et al. 2004). Men and women whose mothers had high intakes of meat and fish and low intakes of green vegetables had raised cortisol concentrations.

Fetal growth and development depends on maternal nutrient stores and the turnover of protein and fat in the mother’s tissues at least as much as on the mother’s diet: for the fetus to depend primarily on the mother’s diet in pregnancy would be too dangerous a strategy (James 1997). Maternal size and body composition account for up to 20% of the variability in birthweight (Catalano et al., 1998). Studies in Europe and India have shown that high maternal weight and adiposity are associated with insulin deficiency, type 2 diabetes and coronary heart disease in
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The ‘developmental origins’ hypothesis: epidemiology

The offspring (Forsen et al. 1997, Fall et al. 1998, Shiell et al. 2001). In the data from Helsinki, increasing maternal body mass index had little effect on the offspring’s death rates in tall women, but strong effects in short women (Forsen et al. 1997). One interpretation of these findings is that greater maternal body fatness may increase fetal growth and hence the fetal demand for nutrients; short women may not be able to meet this increased demand as a result of a constrained nutrient supply capacity determined during their own intrauterine development. These observations for high maternal weight and adiposity add to those linking gestational diabetes with adverse long-term outcomes in the offspring (Silverman et al. 1996).

Of considerable importance is an increasing body of consistent evidence showing strong links between low maternal weight and body mass index and insulin resistance in the adult offspring (Ravelli et al. 1998, Shiell et al. 2000, Mi et al. 2000). Although low maternal body mass index does not appear to be linked with raised blood pressure in the offspring, thin maternal skinfold thicknesses and low pregnancy weight gain have been consistently associated with raised offspring blood pressure (Margetts et al. 1991, Godfrey et al. 1994b, Clark et al. 1998, Adair et al. 2001). One of the metabolic links between maternal body composition and birth size is protein synthesis. Women with a greater lean body mass have higher rates of protein synthesis in pregnancy (Duggleby and Jackson 2001). Variation in rates of maternal protein synthesis explains around a quarter of the variability in birth length.

Prevention of adult degenerative disease

The experimental and epidemiological evidence indicates that prevention of a substantial proportion of degenerative disease, including cardiovascular disease, type 2 diabetes, cognitive decline and osteoporosis, together with obesity, may depend on interventions at a number of stages of development. Strategies that target infants and young children may give the most immediate benefit, but improving the intrauterine environment is an important long-term goal. In mothers we need to improve the macronutrient balance and micronutrient content of the diet before and during pregnancy. Animal studies now show how effective such measures can be in improving the development of the offspring (Brawley et al. 2004). We also need to improve women’s body composition before pregnancy, with avoidance of excessive thinness or overweight. In infants we need to protect growth in weight, length and head circumference during the first year after birth by good infant feeding practices, avoidance of recurrent infections, and cognitive stimulation. We need to prevent rapid weight gain among children especially those who were small or thin at birth or at one year. Adults who were small at birth are more vulnerable to obesity and psychosocial stress in adult life: we need to understand this more deeply in order to prevent it.

The complexities of fetal growth and development are such that currently available data form only a limited basis for changing dietary recommendations to young women. Future work will need to identify the factors that set the trajectory of fetal growth, and the influences that limit the maternoplacental delivery of nutrients and oxygen to the fetus. We also need to define how the fetus adapts to a limited nutrient supply, how these adaptations change the structure and physiology of the body, and by what molecular mechanisms nutrients and hormones alter gene expression. A strategy of interdependent clinical, animal and epidemiological research is required to identify specific recommendations both for whole populations and for vulnerable groups such as teenage pregnancies and single parents. Research is also required to identify the barriers to healthy eating among young women, whose diets are important both for their own health and for the health of the next generation. Such an approach may allow us to reduce the prevalence of major chronic diseases and diminish social inequalities in health.

If, as we believe, a woman’s own fetal growth, and her diet and body composition before and during pregnancy, play a major role in programming the future health of her children, mothers will want to know what they can do to optimise
the intrauterine environment they provide for their babies. A recent technical consultation organised by the United States Department of Agriculture, the World Bank and UNICEF concluded that a key area of focus to reduce the burden of low birthweight and its associated morbidities is to improve the nutritional status of adolescent girls and of pregnant women. Similarly, one of the two main recommendations of an Independent Inquiry into Inequalities in Health (1998) in the United Kingdom was that ‘a high priority is given to policies aimed at improving health and reducing inequalities in women of childbearing age, expectant mothers and young children.’

Conclusion

Degenerative diseases, including cardiovascular disease, type 2 diabetes, osteoporosis and obstructive airways disease, have higher rates among poorer people and cause much disability in both developed and developing communities. The evidence that links the combination of poor maternal nutrition, impaired fetal/infant development and increased weight gain in early childhood to later cardiovascular disease is now strong. Many women have diets with a suboptimal balance of nutrients, and wide variations between women in the amounts of lean and fat tissue alter the partitioning of food between mothers and babies. However, little is known about how maternal nutrition influences early growth and development, or about interactions with genetic influences and with nutrition and physical activity after birth. In order to improve the health of future generations we need to identify the factors that now affect fetal, infant and childhood growth and development.

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The conceptual basis for the developmental origins of health and disease

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Introduction

The fundamental assumption underlying the DOHaD model is that environmental factors acting in early life have consequences which become manifest as an altered disease risk in later life. The concept that multiple phenotypes can arise during development from a single genotype (‘developmental plasticity’) is not new: these different phenotypes are based on the nature of the gene–environment interactions, a feature well recognised in developmental biology and the range of phenotypes that can be induced is termed the reaction norm (Gilbert 2001). Given the universality of developmental plasticity, particular sets of phenotypic outcomes may be manifest as variable disease risk (Bateson et al. 2004). As a result, one part of the reaction norm may be associated with better survival in one type of environment, while another is better suited to a different environment. One example comes from the desert locust \textit{Schistocerca gregaria}, where factors acting in the \textit{larval} stage induce a phenotype appropriate for migratory or non-migratory situations (Applebaum and Heifetz 1999, Simpson \textit{et al.}, 2002). Having a wing shape appropriate for a non-migratory lifestyle will compromise the locust in a situation of overcrowding and nutritional compromise.

While in comparative biology the concept of environmentally influenced developmental trajectories has been accepted, its influence on our understanding of human disease has taken time to be accepted. This delay has impacted on how the developmental-origins field has developed since the early epidemiological observations in humans relating birth size to later disease risk (Forsdahl 1977, Barker and Osmond 1986).

It is now generally accepted that the original observations relating birth size to later disease risk were not due to a causal pathway whereby being small directly caused disease. Rather, the statistical relationship existed because altered birth size is one measure of a disturbed fetal environment. As reviewed in Chapter 1, it is now apparent that the period of early life in which external factors can influence biology extends at least from conception to the neonatal period (Kwong \textit{et al.} 2000, Singhal \textit{et al.} 2003, 2004, Bloomfield \textit{et al.} 2004). Moreover, through the course of human evolution one generally did not live long past the post-reproductive years; hence, there would have been little selection pressure against any processes that had deleterious effects in later life, provided that they conferred fitness earlier in life. Thus, comparative biology and human evolutionary history provide examples of the phenomenon that early-life environmental factors can have lifelong effects and can manifest as disease in modern society. Contemporary human observations must be reinterpreted in view of this understanding.
While the focus of this chapter must be on the mammal and how influences on pregnancy have consequences for the progeny, there is ample evidence of comparable transgenerational influences even in non-mammalian species. These are generally called **maternal effects**, and can be demonstrated in organisms ranging from plants to mammals (Agrawal et al. 1999). If such observations are relevant to DOHaD, and we would propose that they are, then they imply a broader evolutionary importance to the phenomenon.

**Developmental disruption and developmental plasticity**

Developmental plasticity can act early in life to change the course of development, leading to irreversible trajectories that manifest as different phenotypes. These may be very distinct, as in the axolotl, which chooses to be either aquatic or amphibious depending on the availability and size of freshwater ponds during early development (Wolpert 2002). Alternatively, the range of phenotypes may be continuous, as in the case of the timing of metamorphosis in toads, which is determined by population density in the pond (Denver 1997). The greater the population density, the earlier the spade toad will metamorphose from a tadpole to a toad and end its aquatic existence. In the tiger snake, jaw size is matched to prey size a feature determined not by genetics but by exposure during the neonatal phase to prey of different sizes. This matches prey resources to the capacity to eat the prey and demonstrates the adaptive value of phenotypic plasticity (Aubret et al. 2004).

Developmental plasticity is the term that encompasses these physiologically and environmentally determined patterns of development (West-Eberhard 2003, Bateson et al. 2004). Three characteristics are important in understanding developmental plasticity. First, the nature of the response will in part be dependent on the nature of the environmental cue. Second, there are critical windows for plasticity in different systems (i.e., when a system may be most vulnerable to change) that relate, in turn, to the necessary order of development. For instance, an environmental influence may have a lifelong impact if the cue acts during the critical developmental window, but will not have analogous effect if acting outside this window. The neonatal rat brain provides a well-known example of a critical window in development in that exposure to testosterone determines lifelong sexual behaviours (Christensen and Gorski 1978, Jacobson et al. 1981). Third, the duration of developmental plasticity is time-limited: once organogenesis is complete structurally and functionally, plasticity is no longer possible. The timing will be different for different systems and it would appear that the span over which developmental plasticity operates is longer for processes associated with growth and metabolism, as in, for example, the brain versus organs such as the heart. Presumably indefinite plasticity is not realistic because of the energetics required to support it in all tissues and structures.

However, not all environmental factors act during early development through these plastic processes (Gluckman et al. 2005a). Some environmental influences are clearly pathological and lead to disruption of development rather than channelling development. Teratogenesis is the most obvious manifestation of pathology, whereby an environmental toxin may grossly disrupt development with anatomic malformation as the consequence. The organism either dies or is left to cope with the consequences.

Teratogenesis or developmental disruption may also occur at a less overt level. The change may not be in gross structure, leading to a malformation, but in the substructure or function of the organ. This change in structure or function has no adaptive value at any stage in the organism's life – evident, for example, in the functional consequences of intrauterine iodine deficiency leading to hearing impairment (Valeix et al. 1994). The key point here is that some environmental factor induces a developmental change that has no adaptive advantage for the organism. Another example is the reduced
neuronal number found in the hippocampus of animals born with fetal growth retardation (Mallard et al. 2000). It is difficult to conceive of a situation where a reduced number of neurons could be advantageous, yet the growth-retarded animal must cope with the consequences.

This discussion has important implications. One limitation of animal experiments is that when an environmental stress imposed during development is extreme (e.g., following very severe nutritional challenges or very high-dose glucocorticoid exposure), it may be inducing a teratogenic effect. The relevance of such disruptive consequences to the DOHaD phenomenon seems remote. Similarly, the extrapolation from observations made on severely growth-retarded children or prematurely delivered children to the biology of programming must be done with caution. The possibility that an abnormal phenotype represents some form of developmental disruption must be considered. The seminal observations on programming were made on children with birth phenotypes within the normal range, not with extreme abnormal phenotypes. We would argue that phenomena acting across the broad range of the normal population are unlikely to be underpinned by non-regulated disruptive processes.

**Adaptive responses during development**

The developing organism can respond to its environment with transient, homeostatic responses; these do not change its developmental trajectory and are generally only of immediate consequence. This is clearly evident in the developing fetus who in the process of brief periods of asphyxial insult experiences a transient cessation of breathing movements. This type of response has immediate adaptive value in that it allows the fetus to conserve oxygen by stopping an activity that has no survival consequences. However, if the environmental stimulus is chronic or repeated, then transient homeostatic responses may not be sufficient and the trajectory of development may have to change. This process was termed homeorhesis by Waddington (1957). If the trajectory chosen has immediate adaptive advantage but is followed by long-term cost, then a trade-off has been created.

The concept of biological trade-offs is the basis of life-history theory. Trade-offs are common, particularly between growth, reproduction and longevity. For example, under conditions of nutritional stress many invertebrate and vertebrate species will grow more slowly, but enter puberty/reproductive competence earlier (Ibáñez et al. 2000a, Metcalfe and Monaghan 2003). A biological trade-off is a way to survive an environmental challenge with immediate adaptive advantage but long-term disadvantage – but it is only a successful strategy if the species lives long enough to reproduce. Lifelong stunting after a period of intrauterine growth retardation due to maternal undernutrition is such a trade-off. It has clear advantage to the fetus in that it can survive to birth on lesser nutritional support and still reach reproductive competence. The disadvantage is a lesser chance of reproductive success and a greater chance of earlier death, as it has been observed that smaller members of a species may have lesser survival and lower social status in pecking orders that influence reproductive opportunities (Albon et al. 1987, Metcalfe and Monaghan 2003), with strikingly similar observations in humans (Phillips et al. 2001). Premature delivery in response to maternal undernutrition can be demonstrated in many species, including humans (Bloomfield et al. 2003, King 2003, Kramer 2003). This is a form of trade-off by which exit from a potentially dangerous situation of maternal food deprivation allows the organism to be more likely to able to obtain food postnatally. The trade-off is the compromise to health that arises from prematurity.

The ‘thrifty phenotype’ hypothesis, one of the first models developed to explain the DOHaD phenomenon, is based on trade-off theory (Hales and Barker 1992). In brief, it describes how the fetus grows more slowly in response to a deprived intrauterine environment, the consequence of which is an altered biology that the organism must then cope with postnatally. This trade-off contributes to increased
disease risk in later life. This model, which was a valuable step in the development of our current understanding, will be discussed later in this chapter.

More recently we have pointed out that there is a further class of environmental response that is unique to the phase of developmental plasticity, whereby the adaptive advantage is not immediate, but occurs later in life. This type of response is termed a predictive adaptive response (PAR) (Gluckman and Hanson 2004a, 2005). In the desert locust, the choice of wing and metabolic phenotype is determined in the larval phase in response to a pheromonic signal from the mother at egg-laying about population density. The wing shape and metabolism will be set for a migratory form if the population density is high and for the solitary non-migratory form if the density is low (Applebaum and Heifetz 1999, Simpson et al. 2002). Clearly, the choice of wing shape has no advantage to the larva, but is a response for future advantage to an environmental cue about population density. Mammals experience PARs as well, as evident in the meadow vole. The vole pup is born with a coat thickness that is thick if winter is approaching and thin if summer is approaching (Lee and Zucker 1988). Yet the fetal thermal environment and nest temperatures are similar. It has been shown that coat thickness is determined in response to the maternal melatonin cycle (Lee et al. 1989). There can be no advantage to the fetal or infant vole in either trajectory of hair density, but by making a choice in expectation of the future environment the developing vole has an adaptive advantage: it is more likely to survive the oncoming winter or summer, depending on its coat thickness, and successfully reproduce.

PARs have a number of characteristics (see Box 3.1). Using the processes of developmental plasticity, the organism establishes a mature phenotype it expects will be advantageous in the adult environment it predicts to be exposed to (Bateson 2001, Gluckman and Hanson 2004a). The developmental path chosen need not have any immediate adaptive value, as the consequences to the organism depend on the accuracy of the prediction. If the meadow vole was transported to an environment for which the coat thickness was inappropriate, then the vole’s fitness would be compromised.

**Box 3.1 The characteristics of predictive adaptive responses**

- Predictive adaptive responses are induced by environmental factors acting in early life, most often in pre-embryonic, embryonic or fetal life, not as an immediate physiological adaptation, but as a predictive response in expectation of some future environment.
- Predictive adapted responses are manifest in permanent change in the physiology of the organism and are likely underpinned by epigenetic processes.
- There are multiple pathways to the induction of these responses involving different environmental cues acting at different times in development.
- Predictive adaptive responses are not restricted in direction and occur across the full range of fetal environments.
- The induction of predictive adaptive responses will confer a survival advantage in the predicted reproductive environment (that is, appropriate prediction) and this will be manifest as increased fitness.
- The predictive adaptive response thus defines an environmental range in which the organism can optimally thrive until and through the reproductive phase of its postnatal life.
- Predictive adaptive responses may well lead to disease or disadvantage when the predicted reproductive or post-reproductive environmental boundaries are exceeded (that is, inappropriate prediction).
- These responses are neo-Darwinian adaptations permitting a species to survive short-term environmental challenges whilst preserving maximum genotypic variation for later environmental challenges and evolutionary fitness.
- It is to be anticipated that PARs may operate across several generations, depending for example on the duration of gestation in relation to an environmental change, the time to sexual maturity of offspring, etc.

Modified from Gluckman and Hanson (2005).

There is latitude for some adaptive responses to have both short- and long-term advantage. For example, the choice to have an activated hypothalamic–pituitary–adrenal axis (HPAA) in response to