Birth Defects Research (Part C) 72:300–312 (2004)

REVIEW

Embryonic and Fetal Programming of Physiological Disorders in Adulthood

Christopher Lau* and John M. Rogers

In the past decade, data from numerous epidemiological studies have indicated strong inverse associations between birth weight and risk of coronary heart disease, hypertension, type 2-diabetes, and other diseases in adulthood. The "Barker hypothesis" thus postulates that a number of organ structures and functions undergo programming during embryonic and fetal life. This developmental programming determines the set points of physiological and metabolic responses in adult life. Alterations of nutrient availability during gestation may lead to developmental adaptations, via hormonal maneuvers by the embryo and fetus that readjust these set points. These adaptive measures have short-term benefits to the embryo and fetus, so that the newborn will be better prepared for the adverse environment (e.g., undernutrition). However, adequate nutritional support during postnatal life that enables catch-up growth may create metabolic conflicts that predispose the adult to aberrant physiological functions and, ultimately, increased risk of disease. It is plausible that other adverse in utero conditions, including exposure to developmental toxicants, may similarly alter adult disease susceptibility. This article provides an overview of the Barker hypothesis, its supporting evidence, the current advances in understanding the biological mechanisms underlying this phenomenon, and its implications for developmental toxicology. **Birth Defects Research (Part C) 72: 300–312, 2004.** **Published 2005 Wiley-Liss, Inc.†**

INTRODUCTION

Teratology is classically defined as the study of abnormal development during embryonic and fetal stages that leads to anatomical malformations, while more recently this has been extended to encompass functional deficits in the immature organism. Indeed, since the seminal works by Warkany and his colleagues in the 1940s (Warkany and Nelson, 1940; Warkany, 1943; Warkany and Schrafenberger, 1947), experimental teratology combined with clinical birth defect research has evolved into a crosscutting discipline involving developmental biologists, geneticists, toxicologists, pediatricians, and epidemiologists. A majority of the extant teratology literature focuses on structural defects induced by an altered intrauterine environment during gestation. While overt structural defects are usually associated with functional deficiency, the reverse is not necessarily true. Biochemical changes induced by prenatal insults that lead to physiological deficits of organ function may not always be accompanied by *detectable* anatomical abnormalities. Hence, in recent decades, considerable attention has been drawn to *functional teratology*, an extension of the investigation beyond morphological examinations to include the evaluations of functional integrity of organ systems (for examples, see Kavlock and Grabowski, 1983; Lau and Kavlock, 1994; Herzyk et al., 2002). Nonetheless, a majority of these

The "Barker hypothesis" postulates that a number of organ structures and associated functions undergo programming during embryonic and fetal life, which determines the set point of physiological and metabolic responses that carry into adulthood.

Christopher Lau and **John M. Rogers** are from the Reproductive Toxicology Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina.

*Correspondence to: Christopher Lau, Mail Drop 67, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711.
E-mail: lau.christopher@epa.gov

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/bdrc.20029

works has focused primarily on the perinatal and early postnatal periods, and long-term follow-up studies are seldom available.

In the early 1990s, a novel hypothesis was advanced by Barker and associates to link nutritional insults during embryonic and fetal development not only to impaired maturation of physiological functions, but also to latent diseases in adulthood (Barker, 1992a; Hales and Barker, 1992). The "Barker hypothesis" postulates that a number of organ structures and associated functions undergo programming during embryonic and fetal life, which determines the set point of physiological and metabolic responses that carry into adulthood. Hence, alterations in embryonic and fetal nutrition, as well as endocrine status during gestation, can result in developmental adaptations that produce permanent structural, physiological, and metabolic changes, thereby predisposing an individual to cardiovascular, metabolic, and endocrine diseases in adult life (Barker, 1992b). This "fetal origins" hypothesis has increasingly gained support in the past decade from both epidemiological studies as well as investigations in animal models. This article will provide a review of the Barker hypothesis, the current advances in understanding, and implications for future teratological evaluations.

MATERNAL NUTRITIONAL STATUS AND ADULT CARDIOVASCULAR DISEASES

In a series of retrospective studies, Barker and coworkers examined the incidence of coronary heart disease in middle and late-life men and women, and correlated that to the body measurements at birth. In one study, the record of 16,000 subjects born in Hertfordshire, England between 1911 and 1930 was traced. Using birth weight as a surrogate indicator of intrauterine growth, Osmond et al. (1993) reported a fall in death rates from coronary heart disease by almost a factor of two, between those who were born at the upper (4.3 kg) and lower (2.5 kg) extremes of weight. Variations of birth weight seen at Hertfordshire did not appear to be associated with differences in social class. Similar results were obtained by Barker et al. (1993a) from another study conducted in Sheffield, England, with men born between 1907 and 1925. It was noted that the subjects who were small at birth (but born at full term), rather than those born prematurely, were at increased risk of coronary heart disease.

Since then, a robust body of epidemiological evidence supports the British findings. In the San Antonio Heart Study, Valdez et al. (1994) examined the prevalence of ischemic heart disease in young adults and compared that to the participants' birth weight. These investigators reported the odds of expressing the disease increased 1.72 times for each tertile decrease in birth weight. These findings were independent of sex, ethnicity, current socioeconomic status, or obesity. In the Caerphilly study, Frankel et al. (1996) followed a cohort of men in South Wales for 10 years, and reported a significant inverse relationship between birth weight and incidence of coronary heart disease. This association was not changed by adjustment for age, social class, marital status, and smoking history. Stein et al. (1996) studied a group of men and women who were born between 1934 and 1954 in and still residing in Mysore, South India, and noted that low birth weight, short birth length, and small head circumference at birth were associated with a raised prevalence of coronary heart disease. The prevalence fell from 11% in people whose birth weights were 2.5 kg or less, to 3% in those whose birth weights were more than 3.1 kg. In the Nurses' Health Study in the United States, Rich-Edwards et al. (1997) followed a large cohort (over 120,000 women) for 16 years, and indicated a moderate but consistent inverse relationship between birth weight and risk of nonfatal cardiovascular disease. Women who had birth weights of 2.5 kg or less had a significantly higher risk (by 23%) of nonfatal cardiovascular disease compared with the rest of the cohort. Consistent with other studies, the association persisted despite adjustment for hypertension, diabetes, raised cholesterol level, height, body mass index, and childhood socioeconomic status. More recently, Barker et al. (2002) carried out a longitudinal study of Finnish men and women born in Helsinki between 1924 and 1944, and reported that the combination of small size at birth and during infancy, followed by accelerated weight gain from the ages of three to 11 years, predicted significantly higher cumulative incidence of coronary heart disease, type-2 diabetes, and hypertension.

the combination of small size at birth and during infancy, followed by accelerated weight gain from the ages of three to 11 years, predicted significantly higher cumulative incidence of coronary heart disease, type-2 diabetes, and hypertension.

Besides coronary heart disease, blood pressure in adults has also been found to be inversely related to birth weight. As early as 1988, Gennser et al. (1988) evaluated the hospital records of a small pool of Swedish army conscripts and discovered that the risk of increased diastolic blood pressure in early adult life was significantly higher among those who had been smaller at birth than those whose birth weight had been appropriate for gestational age (odds ratio 3.63). These results were confirmed by another Swedish study with a

larger cohort (Leon et al., 1996), where men who had lower birth weight (<3.25 kg) and were above median adult height were found to have the highest blood pressure. Law et al. (1993) examined the British records of men and women of various ages, and observed that those who had lower birth weight had higher systolic blood pressure. This relationship became stronger with increasing age, such that at ages 64–71 years, systolic pressure decreased by 5.2 mm of Hg for every kilogram increase in birth weight. Curhan et al. (1996) examined the records of over 160,000 women in the Nurses' Health Studies in the United States, and reported an age-adjusted odds ratio for hypertension in the low birth weight category (<2.3 kg) of 1.39–1.43 compared to the average birth weight category (3.9 kg). Correspondingly, a decrease of systolic blood pressure by 0.43 mm of Hg, and of diastolic blood pressure by 0.21 mm of Hg, was noted for each 0.45 kg increase in birth weight. The results of this study were consistent with the British data, although the magnitude of the effect was much smaller. In fact, Huxley et al. (2000) reviewed 80 studies from population cohorts around the world describing the relationship of blood pressure with birth weight, and noted a fall in blood pressure with increased birth weight, and meta-analysis demonstrated an average drop of 2 mm of Hg/kg. Interestingly, postnatal catch-up growth was positively associated with blood pressure, with the highest blood pressures occurring in individuals having low birth weight but high rates of postnatal growth. Results from more recent studies are consistent with these general observations (Eriksson et al., 2000; Adair and Cole, 2003; Singh and Hoy, 2003; Hardy et al., 2004; Fagerberg et al., 2004). In addition, IJzerman et al. (2003) suggested that the increase in blood pressure related to low birth weight might involve an increase in cardiac sympathetic activity.

In order to minimize the potential influence of genetic confounders in the association of fetal weight deficits and adult hypertension, studies were conducted in twin pairs. Poulter et al. (1999) reported a graded inverse relation between differences in birth weight and adult blood pressure in a British cohort of twins. IJzerman et al. (2000) examined the birth records of a Dutch cohort of monozygotic and dizygotic twins, and determined their blood pressure at adolescent age. These investigators reported that intrapair differences in birth weight were negatively and significantly associated with differences in systolic blood pressure, with a regression coefficient of –5.7 mm of Hg/kg of birth weight in the dizygotic but not monozygotic twins, suggesting that genetic factors might play a role in the association between birth weight and blood pressure. In comparison, Christensen et al. (2001a) measured the blood pressure of adolescent twins in the Minnesota Twin Family Study and found a negative association between birth weight and systolic blood pressure in the overall samples, with a regression coefficient of –1.88 mm of Hg/kg. However, in contrast to the IJzerman et al. (2000) study, this effect was more pronounced in the monozygotic twins, with a regression coefficient of –2.44 mm Hg. Indeed, Phenekos (2001) examined prospective twin studies in the United States and Northern Europe, and failed to find evidence to support genetic factors that might predispose low birth weight and adult diseases. Loos et al. (2001) evaluated a women's cohort from the East Flanders Prospective Twin Survey and noted a similar decrease of systolic pressure (by 4.27 mm of Hg) and diastolic pressure (by 2.18 mm of Hg) per kilogram increase in birth weight. It is noteworthy that the values of regression coefficient revealed in these twin studies are quite similar to those reported from singleton adolescents (Huxley et al., 2000).

Epidemiological and clinical studies, therefore, suggest a link between nutritional deprivation in utero, reflected by low birth weight, and latent cardiovascular diseases in adulthood. However, among these studies, the actual maternal and fetal nutritional status was always inferred. Thus, episodes of periodic famine, where the maternal nutritional intakes were better documented, offer a unique opportunity to test the Barker hypothesis. Generally speaking, results from these studies are supportive of the hypothesis in a broad sense, but far from definitive. For instance, study of the health consequences of adults born during the Dutch famine of 1944–1945, when the official daily rations dropped from about 1,800 kcal to 400–800 kcal, revealed that only those exposed to malnutrition during early (but not middle or late) gestation were found to have a higher prevalence of coronary heart disease when compared to better nourished subjects (those born the year before or conceived in the year after the famine), and this effect was independent of birth weight (Roseboom et al., 2000a). It is of interest that substantial effects of the famine on fetal growth (indicated by birth weight, length, and head circumference) were seen only with third trimester exposure (Stein et al., 2004), which may explain the lack of significant birth weight association with the early gestational effects of famine. Alternatively, Roseboom et al. (2000a) contended that because the famine ended abruptly, the women who were malnourished during early pregnancy received adequate nourishment during the later part of pregnancy, thus allowing the fetus to catch up on their growth. It is this subpopulation of adults who had the highest prevalence of coronary heart disease. These investigators surmised that the transition from nutritional deprivation in early gestation to nutritional adequacy later on led to metabolic conflicts that resulted in an increased risk of coronary heart disease. On the other hand, no effect of prenatal exposure to undernutrition on blood pressure was observed in the adult subjects (Roseboom et al., 1999), although a more atherogenic lipid profile was seen in those exposed to famine (Roseboom et al., 2000b).

The Leningrad famine in 1941–1944, where the average daily ration for most of the citizens provided around 300 cal and contained virtually no protein, afforded another case study. Surprisingly, comparison of adult subjects exposed to malnutrition in utero during the siege of Leningrad, to those who were born before the siege and those born outside of the affected area (unexposed groups), revealed no relationship between intrauterine growth and adult cardiovascular disease, blood pressure, or plasma lipid concentrations (Stanner et al., 1997). One plausible explanation for the different findings between these two studies may be the length of the famines (much longer in Leningrad) and the abrupt recovery of nutritional status with the Dutch famine (compared to the long periods of relative food shortage preceding and following the Leningrad siege). Hence, the fetuses and infants in the Netherlands were allowed catch-up growth that could account for the latent coronary heart disease, whereas those in Russia had to adapt to a sustained period of nutritional deprivation and, consequently, avoided any metabolic conflicts in adult life (Stanner and Yudkin, 2001).

INTRAUTERINE GROWTH DEFICIT AND ITS ASSOCIATION WITH TYPE 2 DIABETES AND METABOLIC SYNDROME: THE THRIFTY PHENOTYPE HYPOTHESIS

The association of poverty and malnutrition with infant mortality and disease development is not a novel concept (Forsdahl, 1977; Barker and Osmond, 1986), but it was not until the Hertfordshire study, in which Hales et al. (1991) evaluated the glucose tolerance of 64-year-old men and traced their birth records, that strong correlations between low birth weight and metabolic diseases were derived. These investigators found that those men born weighing less than 2.5 kg were almost seven times more likely to have either impaired glucose tolerance or diabetes than those born weighing more than 4.3 kg. Because a link between hypertension and abnormalities of carbohydrate and lipoprotein metabolism had been suggested previously (Reaven and Hoffman, 1989), Barker et al. (1993b) evaluated the same subjects in the Hertfordshire study and found that the prevalence of the metabolic syndrome fell progressively from those with the lowest birth weights to those with the highest. Indeed, when the current body mass index was adjusted for, the odds ratio for the metabolic syndrome in subjects weighing less than 2.5 kg at birth was 18 in comparison with those weighing more than 4.3 kg. Similar results were obtained in another study conducted with men and women in Preston, England that yielded an odds ratio of 14 (Barker et al., 1993b). By and large, these findings were confirmed by other studies with different populations. Two Swedish studies with elderly men reported an inverse relationship between the prevalence of glucose intolerance and birth weight (Lithell et al., 1996; McKeigue et al., 1998). Rich-Edwards et al. (1999) examined nearly 70,000 women in the Nurses' Health Study in the United States, and noted that birth weight was inversely associated with risk for type 2 diabetes during adulthood; this association was not influenced by ethnicity, childhood socioeconomic status, or adult life style factors. Carlsson et al. (1999) conducted a population-based cross-sectional study of Swedish middle-aged men, and reported that birth weights of less than 3 kg were associated with an odds ratio of 2.3 for diabetes.

it was not until the Hertfordshire study, in which Hales et al. (1991) evaluated the glucose tolerance of 64-year-old men and traced their birth records, that strong correlations between low birth weight and metabolic diseases were derived.

Similar observations were made with the Pima Indian children and young adults (Dabellea et al., 1999; Pettitt and Jovanovic, 2001; Stefan et al., 2004) and among school children in Taiwan (Wei et al., 2003). Interestingly, a U-shape relationship between birth weight and risk of type 2 diabetes was noted in these two case studies. Whether the low and high birth weight subjects may share a common etiology for development of diabetes remains to be clarified. Furthermore, to determine if the link between birth weight and diabetes might involve genetic factors, Iliadou et al. (2004) examined a large cohort of Swedish twins, and reported a significant increase in risk of developing type 2 diabetes for a 1-kg decrease in their mean birth weight (odds ratio 2.13), lending support to malnutrition being a possible factor underlying the in utero programming effect that led to a subsequent increased health risk.

Based on their findings, investigators from the Hertfordshire studies proposed a "thrifty phenotype" hypothesis that suggested a malnourished fetus made adaptive changes in glucose-insulin metabolism (including reduced capacity for insulin secretion and insulin resistance), which were designed to improve survival under conditions of nutritional deprivation (Hales and Barker, 1992). The deficient insulin secretion would not be detrimental to health, had the individuals continued to be malnourished (and remained thin); however, when the nutritional status became adequate or excessive during postnatal periods, physiological conflicts arose as glucose intolerance was triggered by a positive caloric balance. Several studies have confirmed an additive effect of fetal growth restric-

Based on their findings, investigators from the Hertfordshire studies proposed a "thrifty phenotype" hypothesis that suggested a malnourished fetus made adaptive changes in glucose-insulin metabolism (including reduced capacity for insulin secretion and insulin resistance), which were designed to improve survival under conditions of nutritional deprivation (Hales and Barker, 1992).

tion and subsequent obesity in worsening glucose tolerance and insulin sensitivity (reviewed in Petry and Hales, 1999; Hales and Barker, 2001). Indeed, in the thrifty phenotype hypothesis, "catch-up" growth that leads to childhood obesity has been regarded as a key component in the manifestation of latent diseases in adulthood (Hales and Ozanne, 2003); hence, no increase in risk of diabetes for small size at birth was observed without excessive postnatal weight gain (Hypponen et al., 2003). Similarly, Cianfarani et al. (1999) has advanced a "catch-up growth" hypothesis with intrauterine growth retarded (IUGR) children. These researchers postulated a rearrangement of the endocrine system in the third trimester leading to low levels of insulin, insulin-like growth factor (IGF)-1, insulin-like growth factor binding protein (IGFBP)-3, and high levels of growth hormone, IGFBP-1, and IGFBP-2. Shortly after birth, tissues that were chronically depleted of insulin and IGF-1 during fetal life and suddenly exposed to increased levels of these two hormones might counteract their additive insulin-like actions by developing insulin resistance as a metabolic defense mechanism to protect the organism from hypoglycemia. Thus, those IUGR children who showed early and complete recovery from intrauterine growth retardation would be at higher risk for metabolic disorders in adulthood. Recent models, based on multiple-regression analysis of the health outcomes on various birth weights and growth rates, also support the fetal programming effect and the significance of catch-up growth (Cole, 2004; Kuzawa, 2004). Moreover, using a mouse model, Ozanne and Hales (2004) demonstrated that the lifespan of the animal was considerably shortened if the postnatal period of growth was accelerated to make up for the growth deficits in utero; additionally, those mice that were exposed to an obesity-inducing diet after weaning were particularly susceptible to the adverse effects on longevity.

LOW BIRTH WEIGHT AND FUNCTIONAL DEFICIENCY OF OTHER ORGAN SYSTEMS IN ADULTHOOD

In addition to the cardiovascular diseases and diabetes described above, the Barker hypothesis has prompted other investigators to examine if functional deficiency of various organ systems can be similarly linked to impaired fetal growth. Most of these studies have been conducted fairly recently, and the findings are therefore less definitive and uniform. Hinchcliffe et al. (1992) examined the kidneys of stillborn IUGR infants and noted 35% fewer nephrons in this group, compared to the average infants at comparable gestational age. Mackenzie et al. (1996) and Manalich et al. (2000) reported strong correlations between glomerular number (direct) and size (inverse) with low birth weight in human neonates,

Indeed, in the thrifty phenotype hypothesis, "catch-up" growth that leads to childhood obesity has been regarded as a key component in the manifestation of latent diseases in adulthood (Hales and Ozanne, 2003)

and it was reasoned that the shortfall in nephron endowment could be the renal risk factor for hypertension in those of low birth weight. However, Marchand and Langley-Evans (2001) recently raised the possibility that reduced renal reserve and hypertension might merely be coincident, and not causally associated. Hoo et al. (2004) reported that forced expiratory volume of the lung was significantly reduced in the low birth weight infants in the first year of life. In the Hertfordshire study, Barker et al. (1991) noted that the mean forced expiratory volume and forced vital capacity, measurements of function in elderly men, rose with increase in birth weight, independently of smoking habit and social class. Evaluation of another cohort in South India provided very similar results, suggesting that adult lung function is programmed in fetal life (Stein et al., 1997). In addition, Lopuhaa et al. (2000) detected a link between exposure to the Dutch famine in mid- and early gestation and prevalence of obstructive airways disease in adulthood.

McDade et al. (2001) followed the development of thymic function in a cohort from the Philippines and reported that prenatal undernutrition was significantly associated with reduced thymopoietin production, suggesting that the environments during fetal and early infant life

may have long-term implications for immunocompetence and adult disease risk. In contrast, Moore et al. (2001) reported that immune function in rural Gambian children was not related to birth size or prenatal high-energy supplementation, although the investigators pointed out the possibility that the defect related to low birth weight might be in immunologic memory, rather than in the early immune response that was measured in this study. Clark et al. (1996) investigated whether functional alterations of the hypothalamic-pituitary-adrenal (HPA) axis might be associated with cardiovascular diseases and diabetes in the low birth weight adults. They measured the urinary metabolites of glucocorticoid hormones and found an inverse association of metabolite excretion with birth weight. Phillips et al. (2000) provided supporting evidence for a relationship between low birth weight and elevated fasting plasma cortisol concentration (an indicator of HPA activity) in adults; furthermore, men with low birth weight were found to have significantly lower pituitary-adrenal responses to the dexamethasone/corticotrophin releasing hormone test (Ward et al., 2004). However, when Fall et al. (2002) examined the serum cortisol profiles of healthy elderly subjects, they did not find any association between low birth weight and continuously raised cortisol concentration in old age. These investigators deduced that the programming effects on the HPA axis might be on its reactivity, rather than the basal tone of hormone secretion.

The association between low birth weight and reproductive function is more subtle. Cresswell et al. (1997a) followed the elderly women in the Hertfordshire study and noted that the age at menopause was unrelated to birth weight, but it occurred earlier in women who had low weight at one year of age. Adair (2001) examined a cohort of young girls in the Philippines and found that although birth weight alone was not significantly related to age at menarche, girls who were relatively long and thin at birth attained menarche an average of six months earlier than those who were short and thin; this effect was most pronounced among girls with greater than average growth increments in the first six months of life. Supporting evidence may be found in an animal study in which IUGR or food restriction during the preweaning period led to delayed onset of puberty in rats; these effects were not dependent on the achievement of a certain crucial weight of the pups at puberty (Engelbregt et al., 2000). On the other hand, Cresswell et al. (1997b) reported that women with polycystic ovaries were found to have above average birth weight and were born to overweight mothers. McCormack et al. (2003) followed a Swedish cohort of women ($<$50 years old), and found that size at birth was positively associated with rates of breast cancer in premenopausal women. These findings are in general agreement with another study examining a Danish cohort (Ahlgren et al., 2004), and suggest a link between high birth weight and cancer incidence. Together with the U-shape findings of diabetes (association with low and high birth weights) in the Pima Indian and Taiwanese children, the issue of macrosomia and long-term adverse health effects needs to be scrutinized more closely. Adult atherosclerosis (Palinski and Napoli, 2002) and high risk of the development of preeclampsia (Dempsey et al., 2003) have also been tied to low birth weight. Lastly, Thompson et al. (2001) examined an elderly cohort to determine if there was an association between birth weight and the risk of depressive disorders, and noted that the odds ratios for depression among men, but not women, rose incrementally with decreasing birth weight. These investigators suggested a neurodevelopmental etiology of depression and that fetal undernutrition might predispose men to depression through programming of the HPA axis. Additional research will be required to explore this possibility.

INTERGENERATIONAL EFFECTS OF FETAL PROGRAMMING

While the aforementioned epidemiological findings have revealed the fetal origins of latent diseases in adulthood, several provocative studies have extended this programming concept to span the next generation (reviewed in Reusens and Remacle, 2001; Drake and Walker, 2004). The notion of transgenerational effects of pregnancy outcomes is actually not new, and has been discussed previously in an excellent review (Emanuel, 1993). In toxicological studies, residual adverse effects derived from in utero exposure to chemicals (Csaba and Inczefi-Gonda, 1999; Stoll et al., 2003; Newbold, 2004) and ionizing radiation (Dubrova, 2003) have been reported to be passed on to the next generation. To determine whether this phenomenon is extended to fetal programming, Skjærven et al. (1997) examined the birth records of Norwegian women, and reported that a mother's birth weight was strongly associated with the weight of her baby, and maternal birth weight was associated with perinatal survival of her baby for mothers whose birth weights were under 2 kg (odds ratio 2.3). In a follow-up study of men and women whose mother's or father's size at birth was recorded, Barker et al. (2000) reported that the children's birth weight was strongly related to their mother's birth weight, and blood pressure in the adults was lower with increasing mother's birth weight, whereas the father's birth size was not related to the adult offspring's blood pressure. Studying three generations of the British national birth cohort, Hypponen et al. (2004) indicated that the mother's birth weight was the strongest determinant of the offspring's birth weight. Interestingly, this intergenerational birth weight association was not observed for mothers born either very small or very large. Similar to the previous study, the father's birth weight or body mass index did not affect the offspring's birth weight. In comparison, Veena

Barker et al. (2000) reported that the children's birth weight was strongly related to their mother's birth weight, and blood pressure in the adults was lower with increasing mother's birth weight, whereas the father's birth size was not related to the adult offspring's blood pressure.

et al. (2004) reported that the birth weights of both parents could predict the offspring's birth weight equally well in a South Indian cohort, although the mother's body mass index had a greater effect than the father's on the offspring's birth weight. These observations are consistent with a study employing dexamethasone-programmed rats, a model in which fetal exposure to excess glucocorticoid resulted in low birth weight with subsequent adult hyperinsulinemia and hyperglycemia (Drake et al., 2004). These researchers reported that the male offspring of female rats that had been exposed to dexamethasone prenatally, also had reduced birth weight, glucose intolerance, and elevated hepatic gluconeogenic enzyme activity; these effects were resolved in a third generation. In contrast, Rogers et al. (2003) failed to detect any evidence for intergenerational reproductive effects due to prenatal and/or postnatal undernutrition in a mouse model. Despite catch-up growth in the IUGR pups (such that at weaning, their weights were no longer different from that of controls), no significant differences were noted in the average F2 litter size or pup weight at birth. An account for these disparate findings remains to be established.

DISSENTING VIEWS

Despite the mounting evidence to support the Barker hypothesis, this provocative concept is not without its critics (Paneth and Susser, 1995; Huxley et al. 2002; Huxley and Neil, 2004) and discordant findings. Most of these were derived from twin studies, in which no significant correlations were noted between birth measurements and acute myocardial infarction (Hubinette et al., 2001), cardiovascular mortality (Christensen et al., 2001b), or blood pressure (Baird et al., 2001; Nowson et al., 2001; Zhang et al., 2001; Johansson-Kark et al., 2002). Barker (1995) argued that twins were a mixture of proportionately and disproportionately small babies (Leveno et al., 1979), and the prevalence of coronary heart disease might depend on the proportionality of these babies, rather than their size alone. However, de Geus et al. (2001) compared blood pressure of twins with their singleton siblings in the Netherlands, and did not observe any difference in blood pressure between twins and singletons, despite the lower birth weight in the twins. Williams and Poulton (2002) followed the birth size, growth, and blood pressure of a cohort in New Zealand, and found no evidence to suggest that children with a low birth weight who became overweight or obese had extra-high blood pressure. In a prospective longitudinal study, Falkner et al. (2004) also failed to detect significant correlation coefficients of birth weight with all blood pressure measurements.

Another issue of contention is the use of birth weight as a surrogate for intrauterine nutritional deficits that presumably led to fetal growth retardation, a key component linking to the latent diseases in adulthood in the Barker hypothesis. However, with the possible exception of the famine studies where food intake of the populations was

Despite the mounting evidence to support the Barker hypothesis, this provocative concept is not without its critics (Paneth and Susser, 1995; Huxley et al. 2002; Huxley and Neil, 2004) and discordant findings.

recorded, the actual nutritional status of the expecting mothers in the epidemiological studies described above was typically unknown. Symonds et al. (2000), Wilcox (2001), and Morley et al. (2002), in particular, questioned whether birth weight alone was a reliable marker for gestational exposure that increased the risk of adult diseases. These investigators pointed out that low birth weight babies could be produced at high altitudes, but that did not lead to an increase in infant mortality. Babies born of Mexican-American mothers in the United States tended to have lower birth weight compared to non-Hispanic whites, but this subpopulation actually had lower infant mortality rates. Whether the adults born at high altitudes or to Mexican-American heritage are more prone to cardiovascular and metabolic diseases than the average populations, as predicted by the Barker hypothesis, remains to be investigated. Alternatively, other measures of birth size or proportionality may provide better markers of an adverse fetal environment and be more accurately correlated to adult health outcomes. For instance, fetal-placental weight ratio at birth has been suggested as a good predictor of adult diseases (Barker et al., 1990; Godfrey and Robinson, 1998).

In addition to the "thrifty phenotype" concept that relates adult diseases to fetal programming in re-

sponse to adverse intrauterine environment, a role for genetic susceptibility has been suggested by the association of low birth weight with type 2 diabetes and cardiovascular diseases (Hattersley and Tooke; 1999; Lindsay et al., 2000; Stern et al., 2000; Frayling and Hattersley, 2001). These investigators proposed that fetal polygenic genetic factors, involving defects such as mutation, duplication, etc., might lead to increased insulin resistance both in utero and in adult life, and this could produce two phenotypes—a small, thin baby and an adult with insulin resistance and increased risk of hypertension and atherosclerosis, particularly in the presence of obesity. To support this contention, it is generally presumed that birth weight and size would be influenced by both sets of inherited paternal and maternal genetic factors. Specifically, if genes shared by the father and the fetus are functional, then insulin resistance of the father should show an inverse correlation with his child's birth weight, measures of insulin-mediated growth and endothelial function. Polymorphisms of genes associated with insulin resistance should also be correlated to impaired fetal growth. This correlation should be evident both within populations and within families, whereby newborns inheriting an insulin-resistance-associated mutation would be expected to have lower birth weight than their siblings who did not inherit the mutation. Nonetheless, the validity of this alternative explanation for the association of low birth weight and metabolic syndrome is yet to be determined.

SUPPORTING FINDINGS FROM ANIMAL MODELS

Despite skepticism and alternative theories, the Barker hypothesis has slowly gained acceptance over the years (Gillman and Rich-Edwards, 2000; Jaquet et al., 2003). However, research on this novel concept largely based on epidemiological observations is not without its challenges (Lucas, 1998; Gillman, 2002). Among them, the veracity of maternal and fetal nutritional status, and the underlying biological mechanisms linking fetal programming to alterations of physiological functions and responses in adulthood are most prominent. Thus, laboratory animal models that are more amenable to experimental manipulations offer an avenue to further investigation of the Barker hypothesis. Indeed, various models involving dietary, surgical, genetic, and pharmacological interventions have recently been reviewed (Bertram and Hanson, 2001; Ozanne, 2001; Langley-Evans, 2001; Holemans et al., 2003).

Petry et al. (1997) reported that rats exposed to protein restriction during gestation and early postnatal life, and subsequently fed a highly palatable diet to induce obesity, were glucose intolerant, hypertriacylglycerolemic, and hypertensive; these effects were additive,

Results from these experimental models, by and large, substantiated the epidemiological findings, and are described briefly here. Using a rat model, Langley and Jackson (1994) and Langley et al. (1994) reported increased systolic blood pressure and altered glucose tolerance in adults that were exposed to maternal low protein diets during fetal development. Petry et al. (1997) reported that rats exposed to protein restriction during gestation and early postnatal life, and subsequently fed a highly palatable diet to induce obesity were glucose intolerant, hypertriacylglycerolemic, and hypertensive; these effects were additive, suggesting that early protein restriction and later obesity were independent risk factors for the development of hypertension. Ozanne et al. (1998) noted ketosis resistance in rat offspring of protein-malnourished dams, a metabolic condition that has been similarly observed in some forms of human diabetes. Kwong et al. (2000) observed that maternal low protein diet in the rat, during only the preimplantation period (for the first 4.25 days after mating), was sufficient to produce blastocyst abnormalities, low birth weight, altered postnatal growth, and hypertension during adulthood. Lewis et al. (2001, 2002) examined the effects of maternal iron deficiency in the rat, and found that pup weight was reduced at birth and systolic pressure of the offspring was significantly elevated. Negative correlation of birth weight and systolic pressure in the adult offspring was obtained from guinea pigs that were exposed to a mild regimen of maternal undernutrition (85% of ad libitum food intake from four weeks before, and throughout pregnancy) (Kind et al., 2002). Similarly, using a sheep model, Gopalakrishnan et al. (2004) reported an elevation of blood pressure in three-year-old animals that were subjected to maternal undernutrition (50% of ad libitum nutrient intake) throughout pregnancy. Maternal protein restriction was reported to lead to hyperinsulinemia and reduced insulin signaling protein expression in adult rat offspring (Fernandez-Twinn et al., 2004). Prenatal stress was found to induce intrauterine growth restriction that led to glucose intolerance and altered feeding behaviors in the adult rat (Lesage et al., 2004). Without employing any experimental manipulation, Woods and Weeks (2004) selected rat pups whose birth weight was less than 90% of the mean pup weight for the litter, and noted that the blood pressure of the runts was significantly higher than their normal birth weight littermates, and that this relative hypertensive effect was not likely due to gross differences in renal function.

The possible biological mecha-

nisms underlying intrauterine programming of adult diseases have been discussed in recent reviews (Symonds et al., 2001; Bertram and Hanson, 2002; Fowden and Forhead, 2004). A majority of these studies focused on resetting of fetal endocrine homeostasis in response to fetal growth impairment brought forth by maternal nutritional deficits. Several hormones are known to regulate fetal growth and development and may also play a central role in intrauterine programming. These include anabolic hormones such as insulin, insulin-like growth factors (IGF-I and IGF-II), prolactin and thyroid hormones, as well as catabolic hormones such as the glucocorticoids. These hormones act as nutritional and maturational cues, and adapt fetal development to the prevailing intrauterine conditions, thereby maximizing the chances of survival in utero and at birth. However, alterations of these signals in response to an adverse intrauterine environment (such as a deficit of nutrients) will accordingly adjust the set point of these hormones in modulating their functional reactivity in the tissues, as well as regulatory controls of the organ systems. Such endocrine maneuvers may have short-term benefits to the well being of the fetus, but also permanently reset the endocrine systems so as to predispose the adult to aberrant physiological functions and ultimately, disease pathogenesis. Indeed, Plagemann (2004) described these hormones as "endogenous functional teratogens." Alterations of the glucocorticoid hormones and the HPA axis, in particular, have drawn considerable attention, and evidence of their involvement in fetal programming has been discussed in detail in two excellent reviews (Bertram and Hanson, 2002; Fowden and Forhead, 2004). Briefly, their concentrations in utero can be elevated by nutritional perturbation and other stressful insults that are known to have programming effects. These changes of hormone levels are paralleled by altered expression of glucocorticoid receptors (that confer hormonal actions) and the associated genes of receptors, enzymes, ion channels, and transporters that are regulated by the glucocorticoids, as well as ontogenetic deviations of the HPA axis. Hence, these endocrine changes can be both the cause and the consequence of intrauterine programming.

Alternatively, an intriguing epigenetic hypothesis of regulating the intrauterine supply of and demand for nutrients by imprinted genes has been advanced to account for fetal programming (reviewed in Rakyan et al., 2001; Reik et al., 2003; Waterland and Jirtle 2004). Epigenetic control of gene expression involves modification of the genome not involving alterations of the DNA sequence, and is typically mediated by changing the DNA methylation pattern and/or modifications of chromatin packaging via changes in histone acetylation. These mechanisms may influence gene expression by transcriptional silencing of the modified allele (Rakyan et al., 2001) and, therefore, may affect the phenotype without changing the DNA sequence per se. These molecular events are established early in development and maintained throughout life, thus making them prime candidates to account for fetal programming. The seminal work by Waterland and Jirtle (2003), in particular, supports this hypothesis. In this study, the investigators were able to demonstrate that dietary supplementation can dramatically alter the heritable phenotypic changes in agouti mice. Furthermore, the transposon gene involved in this alteration was shown to be imprinted, such that only the maternal contribution was expressed. If the findings with the agouti mouse model are applicable to humans, they may provide a viable mechanism to explain fetal programming via metabolic imprinting that leads to chronic diseases in adult life (Waterland and Jirtle, 1999).

IMPLICATIONS TO DEVELOPMENTAL TOXICOLOGY

An increasing body of evidence from epidemiological observations and studies with various animal models has pointed toward an inverse correlation between low birth weight and latent diseases in adults. A majority, of these studies have presumed that intrauterine malnutrition is the cause of low birth weight. However, in addition to deprivation of nutrients, deficits in fetal growth can also be produced by chemical insults during pregnancy. In fact, the Guidelines for Developmental Toxicity Risk Assessment issued by the U.S. Environmental Protection Agency (1991) state that:

> "A change in offspring body weight is a sensitive indicator of developmental toxicity, in part because it is a continuous variable. In some cases, offspring weight reduction may be the only indicator of developmental toxicity. While there is always a question as to whether weight reduction is a permanent or transitory effect, little is known about the long-term consequences of short-term fetal or neonatal weight changes. Therefore, when significant weight reduction effects are noted, they are used as a basis to establish the NOAEL (no-observed-adverse-effect-level)."

Indeed, several studies have attempted to link toxicant-induced reductions of fetal weight at term to increased incidence of developmental malformations and prenatal death (Ryan et al., 1991; Catalano et al., 1993; Gaylor and Chen, 1993). The question thus arises as to whether the fetal and birth weight deficits induced by developmental toxicants may similarly lead to reprogramming of set points for physiological functions and responses that ultimately lead to cardiovascular and metabolic diseases in adulthood. Naturally, maternal malnutrition itself can be associated with the chemical insult, typically indicated by a transient reduction of maternal food intake. Hence, it is not unreasonable to apply the Barker hypothesis to toxicological investigations. Furthermore, in most toxicological studies, fetal and neonatal weight deficits resulting from chemical exposure in

The question thus arises as to whether the fetal and birth weight deficits induced by developmental toxicants may similarly lead to reprogramming of set points for physiological functions and responses that ultimately lead to cardiovascular and metabolic diseases in adulthood.

utero are transitory, and therefore, have been argued to be innocuous. However, one can also view this "recovery" as catch-up growth during postnatal development, which is a key component to the manifestation of adult diseases in the Barker hypothesis. Does it mean that this population is, in fact, more susceptible to adult diseases and therefore assumes higher health risks? Indeed, the advent of the Barker hypothesis, if proven applicable to toxicant-induced fetal growth impairment, would require reconsideration of the risk assessment guidelines for developmental toxicity. Thus, teratologists may yet have to expand the scope of their research further still, not only to examine the anatomical structure of an organ and its functional maturation, but also to follow potential latent abnormalities of the system into adult age, given that the adult-onset diseases may have their origins in insults during fetal development.

REFERENCES

Adair LS. 2001. Size at birth predicts age at menarche. Pediatrics 107:e59.

Adair LS, Cole TJ. 2003. Rapid child growth raises blood pressure in adolescent boys who were thin at birth. Hypertension 41:451–456.

Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TIA. 2004. Growth patterns and the risk of breast cancer in women. N Engl J Med 351:1619–1626.

Baird J, Osmond C, MacGregor A, et al. 2001. Testing the fetal origins hypothesis in twins: the Birmingham twin study. Diabetologia 44:33–39.

Barker DJ, Osmond C. 1986. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 1:1077–1081.

Barker DJP, Bull AR, Osmond C, Simmonds SJ. 1990. Fetal and placental size and risk of hypertension in adult life. BMJ 301:259–262.

Barker DJ, Godfrey KM, Fall C, et al. 1991. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. BMJ 303:671–675.

Barker DJ. 1992a. The fetal origins of adult hypertension. J Hypertens Suppl 10:S39–S44.

Barker DJP. 1992b. Fetal and infant origins of adult disease. London: BMJ Publishing.

Barker DJP, Osmond C, Simmonds SJ, Wield GA. 1993a. The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life. BMJ 306:422–426.

Barker DJ, Hales CN, Fall CH, et al. 1993b. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia 36:62–67.

Barker DJP. 1995. Fetal origins of coronary heart disease. BMJ 311:171–174.

Barker DJ, Shiell AW, Barker ME, Law CM. 2000. Growth in utero and blood pressure levels in the next generation. J Hypertens 18:843–846.

Barker DJ, Eriksson JG, Forsen T, Osmond C. 2002. Fetal origins of adult disease: strength of effects and biological basis. Int J Epidermiol 31:1235–1239.

Bertram CE, Hanson MA. 2001. Animal models and programming of the metabolic syndrome. Br Med Bull 60:103–121.

Bertram CE, Hanson MA. 2002. Prenatal programming of postnatal endocrine responses by glucocorticoids. Reproduction 124:459–467.

Carlsson S, Persson P-G, Alvarsson M, Efendic S, Norman A, Svanstrom L, Ostenson A-G, Grill V. 1999. Low birth weight, family history of diabetes, and glucose intolerance in Swedish middle-aged men. Diabetes Care 22:1043–1047.

Catalano PJ, Scharfstein DO, Ryan LM, et al. 1993. Statistical model for fetal death, fetal weight, and malformation in developmental toxicity studies. Teratology 47:281–290.

Christensen K, Stovring H, McGue M. 2001a. Do genetic factors contribute to the association between birth weight and blood pressure? J Epidemiol Commun Health 55:583–587.

Christensen K, Wienke A, Skytthe A, et al. 2001b. Cardiovascular mortality in twins and the fetal origins hypothesis. Twin Res 4:344–349.

Cianfarani S, Germani D, Branca F. 1999. Low birthweight and adult insulin resistance: the "catch-up growth" hypothesis. Arch Dis Child Fetal Neonatal Ed 81:F71–F73.

Clark PM, Hindmarsh PC, Shiell AW, et al. 1996. Size at birth and adrenocortical function in childhood. Clin Endocrinol 45:721–726.

Cole TJ. 2004. Modeling postnatal exposures and their interactions with birth size. J Nutr 134:201–204.

Cresswell JL, Egger P, Fall CH, et al. 1997a. Is the age of menopause determined in-utero? Early Hum Dev 49: 143–148.

Cresswell JL, Barker DJP, Osmond C, et al. 1997b. Fetal growth, length of gestation, and polycystic ovaries in adult life. Lancet 350:1131–1135.

Csaba G, Inczefi-Gonda A. 1999. Direct and transgenerational effect of benzpyrene treatment at adolescent age on the uterine estrogen receptor and thymic glucocorticoid receptor of the adult rat. Acta Physiol Hung 86:29–36.

Curhan GC, Chertow GM, Willett WC, et al. 1996. Birth weight and adult hypertension and obesity in women. Circulation 94:1310–1315.

Dabellea D, Pettitt DJ, Hanson RL, et al. 1999. Birth weight, type 2 diabetes, and insulin resistance in Pima Indian children and young adults. Diabetes Care 22:944–950.

de Geus EJ, Posthuma D, IJzerman RG, Boomsma DI. 2001. Comparing blood pressure of twins and their singleton siblings: being a twin does not affect adult blood pressure. Twin Res 4:385–391.

Dempsey JC, Williams MA, Luthy DA, et al. 2003. Weight at birth and subsequent risk of preeclampsia as an adult. Am J Obstet Gynecol 189:494–500.

Drake AJ, Walker BR. 2004. The intergenerational effects of fetal programming: non-genomic mechanisms for the inheritance of low birth weight and cardiovascular risk. J Endocrinol 180:1–16.

Drake AJ, Walker BR, Seckl JR. 2004. Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats. Am J Physiol Regul Integr Comp Physiol 288:R34–R38.

Dubrova YE. 2003. Radiation-induced transgenerational instability. Oncogene 22:7087–7093.

Emanuel I. 1993. Intergenerational factors in pregnancy outcome: implications for teratology? Issues Rev Teratol 6:47–83.

Engelbregt MJT, Houdujk MECAM, Popp-Snijders C, Delemarre-van de Waal HA.

2000. The effects of intra-uterine growth retardation and postnatal undernutrition on onset of puberty in male and female rats. Pediatr Res 48:803–807.

Eriksson J, Forsen T, Tuomilehto J, et al. 2000. Fetal and childhood growth and hypertension in adult life. Hypertension 36:790–794.

Fagerberg B, Bondjers L, Nilsson P. 2004. Low birth weight in combination with catch-up growth predicts the occurrence of the metabolic syndrome in men at late middle age: the Atherosclerosis and Insulin Resistance study. J Intern Med 256:254–259.

Falkner B, Hulman S, Kushner H. 2004. Effect of birth weight on blood pressure and body size in early adolescence. Hypertension 43:203–207.

Fall CHD, Dennison E, Cooper C, et al. 2002. Does birth weight predict adult serum cortisol concentrations? Twenty-four-hour profiles in the United Kingdom 1920–1930 Hertfordshire birth cohort. J Clin Endocrinol Metab 87:2001–2007.

Fernandez-Twinn DS, Wayman A, Ekizoglou S, et al. 2004. Maternal protein restriction leads to hyperinsulinemia and reduced insulin signalling protein expression in 21 month-old female rat offspring. Am J Physiol Regul Integr Comp Physiol (in press).

Forsdahl A. 1977. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? Br J Prev Soc Med 31:91–95.

Fowden AL, Forhead AJ. 2004. Endocrine mechanisms of intrauterine programming. Reproduction 127:515–526.

Frankel S, Elwood P, Sweetnam P, et al. 1996. Birthweight, adult risk factors and incident coronary heart disease: the Caerphilly Study. Public Health 110: 139–143.

Frayling TM, Hattersley AT. 2001. The role of genetic susceptibility in the association of low birth weight with type 2 diabetes. Br Med Bull 60:89–101.

Gaylor DW, Chen JJ. 1993. Dose-response models for developmental malformations. Teratology 47:291–297.

Gennser G, Rymark P, Isberg PE. 1988. Low birth weight and risk of high blood pressure in adulthood. BMJ 296:1498–1500.

Gillman MW, Rich-Edwards J. 2000. The fetal origins of adult disease: from sceptic to convert. Paediatr Perinat Epidemiol 14:192–193.

Gillman MW. 2002. Epidemiological challenges in studying the fetal origins of adult chronic disease. Int J Epidemiol 31:294–299.

Godfrey K, Robinson S. 1998. Maternal nutrition, placental growth and fetal programming. Proc Nutr Soc 57:105–111.

Gopalakrishnan GS, Gardner DS, Rhind SM, et al. 2004. Programming of adult cardiovascular function after early maternal undernutrition in sheep. Am J Physiol Regul Integr Comp Physiol 287: R12–R20.

Hales CN, Barker DJP, Clark PM, et al. 1991. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 303:1019–1022.

Hales CN, Barker DJP. 1992. Type-2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 35:595–601.

Hales CN, Barker DJP. 2001. The thrifty phenotype hypothesis. Br Med Bull 60: 5–20.

Hales CN, Ozanne SE. 2003. The dangerous road of catch-up growth. J Physiol 547:5–10.

Hardy R, Wadsworth MEJ, Langenberg C, Kuh D. 2004. Birthweight, childhood growth, and blood pressure at 43 years in a British birth cohort. Int J Epidermiol 33:121–129.

Hattersley AT, Tooke JE. 1999. The fetal insulin hypothesis: an alternative explanation of the association of low birthweight with diabetes and vascular disease. Lancet 353:1789–1792.

Hinchcliffe SA, Lynch MRJ, Sargent PH, Howard CV, van Zelzen D. 1992. The effect of intrauterine growth retardation on the development of renal nephrons. Br. J. Obstet Gyneae 99: 296–301.

Herzyk DJ, Bugelski PJ, Hart TK, Wier PJ. 2002. Practical aspects of including functional endpoints in developmental toxicity studies. Case study: immune function in HuCD4 transgenic mice exposed to anti-CD4 MAb in utero. Hum Exp Toxicol 21:507–512.

Holemans K, Aerts I, Van Assche FA. 2003. Fetal growth restriction and consequences for the offspring in animal models. J Soc Gynecol Investig 10:392–399.

Hoo AF, Stocks J, Lum S, et al. 2004. Development of lung function in early life: influence of birth weight in infants of nonsmokers. Am J Respir Crit Care Med 170:527–533.

Hubinette A, Cnattingius S, Ekbom A, et al. 2001. Birthweight, early environment, and genetics: a study of twins discordant for acute myocardial infarction. Lancet 357:1997–2001.

Huxley RR, Shiell AW, Law CM. 2000. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systemic review of the literature. J Hypertens 18:815–831.

Huxley R, Neil A, Collins, R. 2002. Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? Lancet 360:659–665.

Huxley RR, Neil HA. 2004. Does maternal nutrition in pregnancy and birth weight influence levels of CHD risk factors in adult life? Br J Nutr 91:459–468.

Hypponen E, Power C, Smith GD. 2003. Prenatal growth, BMI, and risk of type 2 diabetes by early midlife. Diabetes Care 26:2512–2527.

Hypponen E, Power C, Smith GD. 2004. Parental growth at different life stages and offspring birthweight: an intergenerational cohort study. Paediatr Perinat Epidemiol 18:168–177.

IJzerman RG, Stehouwer CDA, Boomsma DI. 2000. Evidence for genetic factors explaining the birth weight–blood pressure relation. Analysis in twins. Hypertension 36:1008–1012.

IJzerman RG, Stehouwer CDA, de Geus EJ, et al. 2003. Low birth weight is associated with increased sympathetic activity: dependence on genetic factors. Circulation 108:566–571.

Iliadou A, Cnattinglus S, Lichtenstein P. 2004. Low birthweight and Type 2 diabetes: A study on 11,162 Swedish twins. Int J Epidemiol 33:1–6.

Jaquet D, Leger J, Levy-Marchal C, Czernichow P. 2003. Low birth weight: effect on insulin sensitivity and lipid metabolism. Horm Res 59:1–6.

Johansson-Kark M, Rasmussen F, De Stavola B, Leon DA. 2002. Fetal growth and systolic blood pressure in young adulthood: the Swedish Young Male Twins Study. Paediatr Perinat Epidemiol 16:200–209.

Kavlock RJ, Grabowski CT. 1983. Abnormal functional development of the heart, lungs, and kidneys. Approaches to functional teratology. New York: Alan R. Liss.

Kind KL, Simonetta G, Clifton PM, et al. 2002. Effect of maternal feed restriction on blood pressure in the adult guinea pig. Exp Physiol 87:469–477.

Kuzawa CW. 2004. Modeling fetal adaptation to nutrient restriction: testing the fetal origins hypothesis with a supply-demand model. J Nutr 134:194–200.

Kwong WY, Wild AE, Roberts P, et al. 2000. Maternal undernutrition during the preimplantation period of rat development causes blastocyst abnormalities and programming of postnatal hypertension. Development 127:4195–4202.

Langley SC, Jackson AA. 1994. Increased systolic blood pressure in adult rats induced by fetal exposure to maternal low protein diets. Clin Sci 86:217–222.

Langley SC, Browne RF, Jackson AA. 1994. Altered glucose tolerance in rats exposed to maternal low protein diets in utero. Comp Biochem Physiol Physiol 109:223–229.

Langley-Evans SC. 2001. Fetal programming of cardiovascular function through exposure to maternal undernutrition. Proc Nutr Soc 60:505–513.

Lau C, Kavlock RJ. 1994. Functional toxicity of the developing heart, lung and kidney. In: Kimmel CA, Buelke-Sam J, editors. Developmental toxicology. 2nd ed. New York: Raven Press, New York. pp. 119–188.

Law CM, de Swiet M, Osmond C, et al. 1993. Initiation of hypertension in utero and its amplification throughout life. BMJ 306:24–27.

Leon DA, Koupilova I, Lithall HO, et al. 1996. Failure to realize growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men. BMJ 312:401–406.

Lesage J, Del-Favero F, Leonhardt M, et al. 2004. Prenatal stress induces intrauterine growth restriction and programmes glucose intolerance and feeding behaviour disturbances in the aged rat. J Endocrinol 181:291–296.

Leveno KJ, Santos-Ramos R, Duenhoelter JH, et al. 1979. Sonar cephalometry in twins: a table of biparietal diameters for normal twin fetuses and a comparison with singletons. Am J Obstet Gynecol 135:727–730.

Lewis RM, Petry CJ, Ozanne SE, Hales CN. 2001. Effects of maternal iron restriction in the rat on blood pressure, glucose tolerance, and serum lipids in the 3-month-old offspring. Metabolism 50:562–567.

Lewis RM, Forhead AJ, Petry CJ, et al. 2002. Long-term programming of blood pressure by maternal dietary iron restriction in the rat. Br J Nutr 88:283–290.

Lindsay RS, Dabelea D, Roumain J, et al. 2000. Type 2 diabetes and low birth weight: the role of paternal inheritance in the association of low birth weight and diabetes. Diabetes 49:445–449.

Lithell HO, McKeigue PM, Bergland L, et al. 1996. Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50–60 years. BMJ 312:406–410.

Loos RJF, Fagard R, Beunen G, et al. 2001. Birth weight and blood pressure in young adults. A prospective twin study. Circulation 104:1633–1638.

Lopuhaa CE, Roseboom TJ, Osmond C, et al. 2000. Atopy, lung function, and obstructive airways disease after prenatal exposure to famine. Thorax 55: 555–561.

Lucas A. 1998. Programming by early nutrition: an experimental approach. J Nutr 128:401S–406S.

Mackenzie HS, Lawler EV, Brenner BM. 1996. Congenital oligonephropathy: the fetal flaw in essential hypertension. Kidney Int Suppl 55:S30–S34.

Manalich RM, Reyes L, Herrera M, et al. 2000. Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. Kidney Int 58:770–773.

Marchand MC, Langley-Evans SC. 2001. Intrauterine programming of nephron number: the fetal flaw revisited. J Nephrol 14:327–331.

McCormack VA, dos Santos Silva I, De Stavola BL, et al. 2003. Fetal growth and subsequent risk of breast cancer: results from long term follow up of Swedish cohort. BMJ 326:248–253.

McDade TW, Beck MA, Kuzawa CW, Adair LS. 2001. Prenatal undernutrition and postnatal growth are associated with adolescent thymic function. J Nutr 131: 1225–1231.

McKeigue PM, Lithell HO, Leon DA. 1998. Glucose tolerance and resistance to insulin-stimulated glucose uptake in men aged 70 years in relation to size at birth. Diabetologia 41:1133–1138.

Moore SE, Collinson AC, Prentice AM. 2001. Immune function in rural Gambian children is not related to season of birth, birth size, or maternal supplementation status. Am J Nutr 74:840–847.

Morley R, Owens J, Blair E, Dwyer T. 2002. Is birthweight a good marker for gestational exposures that increase the risk of adult disease? Paediatr Perinat Epidemiol 16:194–199.

Newbold RR. 2004. Lessons learned from perinatal exposure to diethylstilbestrol. Toxicol Appl Pharmacol 199:142–150.

Nowson CA, MacInnis RJ, Hopper JL, et al. 2001. Association of birth weight and current body size to blood pressure in female twins. Twin Res 4:378–384.

Osmond C, Barker DJP, Winter PD, et al. 1993. Early growth and death from cardiovascular disease in women. BMJ 307: 1519–1524.

Ozanne SE, Wang CL, Petry CJ, et al. 1998. Ketosis resistance in the male offspring of protein-malnourished rat dams. Metabolism 47:1450–1454.

Ozanne SE. 2001. Metabolic programming in animals. Br Med Bull 60:143–152.

Ozanne SE, Hales CN. 2004. Lifespan: catch-up growth and obesity in male mice. Nature 427:411–412.

Palinski W, Napoli C. 2002. The fetal origins of atherosclerosis: maternal hypercholesterolemia, and cholesterol-lowering or antioxidant treatment during pregnancy influence in utero programming and postnatal susceptibility to atherogenesis. FASEB J 16:1348–1360.

Paneth N, Susser M. 1995. Early origin of coronary heart disease (the "Barker hypothesis"). BMJ 310:411–412.

Petry CJ, Ozanne SE, Wang CL, Hales CN. 1997. Early protein restriction and obesity independently induce hypertension in 1-year-old rats. Clin Sci 93: 147–152.

Petry CJ, Hales CN. 1999. Intrauterine development and its relationship with type 2 diabetes mellitus. In: Hitman GA, editors. Type 2 diabetes: prediction and prevention. Chichester, UK: John Wiley & Sons. pp. 153–168.

Pettitt DJ, Jovanovic L. 2001. Birth weight as a predictor of type 2 diabetes mellitus: the U-shaped curve. Curr Diab Rep 1:78–81.

Phenekos C. 2001. Influence of fetal body weight on metabolic complications in adult life: review of the evidence. J Pediatr Endocrinol Metab 14(Suppl 5): 1361–1363.

Phillips DIW, Walker BR, Reynolds RM, et al. 2000. Low birth weight predicts elevated plasma cortisol concentrations in adults from 3 populations. Hypertension 35:1301–1306.

Plagemann A. 2004. 'Fetal programming' and 'functional teratogenesis': on epigenetic mechanisms and prevention of perinatally acquired lasting health risks. J Perinat Med 32:297–305.

Poulter NR, Chang CL, MacGregor AJ, et al. 1999. Association between birth weight and adult blood pressure in twin: historical cohort study. BMJ 319:1330–1333.

Rakyan VK, Preis J, Morgan HD, Whitelaw E. 2001. The marks, mechanisms and memory of epigenetic states in mammals. Biochem J 356:1–10.

Reaven GM, Hoffman BB. 1989. Hypertension as a disease of carbohydrate and lipoprotein metabolism. Am J Med 87:25–68.

Reik W, Constancia M, Fowden A, et al. 2003. Regulation of supply and demand for maternal nutrients in mammals by imprinted genes. J Physiol 547:35–44.

Reusens B, Remacle C. 2001. Intergenerational effect of an adverse intrauterine environment on perturbation of glucose metabolism. Twin Res 4:406–411.

Rich-Edwards JW, Stampfer MJ, Manson JE, et al. 1997. Birthweight and risk of cardiovascular disease in a cohort of women followed up since 1976. BMJ 315:396–400.

Rich-Edwards JW, Colditz GA, Stampfer MJ, et al. 1999. Birthweight and the risk for type 2 diabetes mellitus in adult women. Ann Intern Med 130:278–284.

Rogers EH, Hunter ES, Rosen MB, et al. 2003. Lack of evidence for intergenerational reproductive effects due to prenatal and postnatal undernutrition in the female CD-1 mouse. Reprod Toxicol 17:519–525.

Roseboom TJ, van der Meulen JH, Ravelli AC, et al. 1999. Blood pressure in adults after prenatal exposure to famine. J Hypertens 17:325–330.

Roseboom TJ, van der Meulen JHP, Osmond C, et al. 2000a. Coronary heart disease after prenatal exposure to the Dutch famine, 1944–45. Heart 84:595–598.

Roseboom TJ, van der Meulen JHP, Osmond C, et al. 2000b. Plasma lipid profiles in adults after prenatal exposure to the Dutch famine. Am J Clin Nutr 72:1101–1106.

Ryan LM, Catalano PJ, Kimmel CA, Kimmel GL. 1991. Relationship between fetal weight and malformation in developmental toxicity studies. Teratology 44:215–223.

Singh GR, Hoy WE. 2003. The association between birthweight and current blood pressure: a cross-sectional study in an Australian Aboriginal community. Med J Aust 179:532–535.

Skjærven R, Wilcox AJ, Øyen N, Magnus P. 1997. Mother's birth weight and survival of their offspring: population based study. BMJ 314:1376–1380.

Stefan N, Weyer C, Levy-Marchal C, et al. 2004. Endogenous glucose production, insulin sensitivity, and insulin secretion in normal glucose-tolerant Pima

Indians with low birth weight. Metabolism 53:904–911.
Stanner SA, Bulmer K, Andres C, et al. 1997. Does malnutrition in utero determine diabetes and coronary heart disease in adulthood? Results from the Leningrad siege study, a cross section study. BMJ 315:1342–1348.
Stanner SA, Yudkin JS. 2001. Fetal programming and the Leningrad siege study. Twin Res 4:287–292.
Stein CE, Fall CHD, Kumaran K, et al. 1996. Fetal growth and coronary heart disease in South India. Lancet 348: 1269–1273.
Stein CE, Kumaran K, Fall CH, et al. 1997. Relation of fetal growth to adult lung function in South India. Thorax 52:895–899.
Stein AD, Zybert PA, van de Bor M, Lumey LH. 2004. Intrauterine famine exposure and body proportions at birth: the Dutch Hunger Winter. Int J Epidemiol 33:831–836.
Stern MP, Bartley M, Duggirala R, Bradshaw B. 2000. Birth weight and the metabolic syndrome: thrifty phenotype or thrifty genotype? Diabetes Metab Res Rev 16:88–93.
Stoll C, Alembik Y, Dott B. 2003. Limb reduction defects in the first generation and deafness in the second generation of intrauterine exposed fetuses to diethylstilbestrol. Ann Genet 46:459–465.
Symonds ME, Budge H, Stephenson T. 2000. Limitation of models used to examine the influence of nutrition during pregnancy and adult disease. Arch Dis Child 83:215–219.
Symonds ME, Budge H, Stephenson T, McMillen IC. 2001. Fetal endocrinology and development—manipulation and adaptation to long-term nutritional and environmental challenges. Reproduction 121:853–862.
Thompson C, Syddall H, Rodin I, Osmond C, Braker DJP. 2001. Birth weight and the risk of depressive disorder in later life. Br J Psychiatry 179:450–455.
U.S. Environmental Protection Agency. 1991. Guidelines for developmental toxicity risk assessment. Fed Regist 56(234):63798–63826.
Valdez R, Athens MA, Thompson GH, Bradshaw BS, Stern MP. 1994. Birthweight and adult health outcomes in a biethnic population in the USA. Diabetologia 37:624–631.
Veena SR, Kumaran K, Swarnagowri MN, et al. 2004. Intergenerational effects on size at birth in South India. Paediatr Perinat Epidemiol 18:361–370.
Ward AM, Syddall HE, Wood PJ, et al. 2004. Fetal programming of the hypothalamic-pituitary-adrenal (HPA) axis: low birth weight and central HPS regulation. J Clin Endocrinol Metab 89: 1227–1233.
Warkany J, Nelson RC. 1940. Appearance of skeletal abnormalities in the offspring of rats reared on a deficient diet. Science 92:383–384.
Warkany J. 1943. Effect of maternal rachitogenic diet on skeletal development of young rat. Am J Dis Child 66:511.
Warkany J, Schraffenberger E. 1947. Congenital malformations induced in rats by roentgen rays. Am J Roentgenol Radium Ther 57:455–463.
Waterland RA, Jirtle RA. 1999. Potential mechanisms of metabolic imprinting that lead to chronic disease. Am J Clin Nutr 69:179–197.
Waterland RA, Jirtle RA. 2003. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. Mol Cell Biol 23:5293–5300.
Waterland RA, Jirtle RA. 2004. Early nutrition, epigenetic changes at transposons and imprinted genes, and enhanced susceptibility to adult chronic diseases. Nutrition 20:63–68.
Wei JN, Sung FC, Li CY, et al. 2003. Low birth weight and high birth weight infants are both at an increased risk to have type 2 diabetes among school children in Taiwan. Diabetes Care 26:343–348.
Wilcox AJ. 2001. On the importance—and the unimportance—of birthweight. Int J Epidemiol 30:1233–1241.
Williams S, Poulton R. 2002. Birth size, growth, and blood pressure between the ages of 7 and 26 years: failure to support the fetal origins hypothesis. Am J Epidemiol 155:849–852.
Woods LL, Weeks DA. 2004. Naturally occurring intrauterine growth retardation and adult blood pressure in rats. Pediatr Res 56:763–767.
Zhang J, Brenner RA, Klebanoff MA. 2001. Differences in birth weight and blood pressure at age 7 years among twins. Am J Epidemiol 53:779–782.