Prenatal origins of adult disease

Mark J. Nijland[a,b], Stephen P. Ford[b] and Peter W. Nathanielsz[a,b]

[a]Center for Pregnancy and Newborn Research, Department of Obstetrics and Gynecology, University of Texas Health Science Center at San Antonio, San Antonio, Texas and [b]Center for the Study of Fetal Programming, Department of Animal Sciences, University of Wyoming, Laramie, Wyoming, USA

Correspondence to Peter W. Nathanielsz, MD, PhD, Department of Obstetrics and Gynecology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA
Tel: +1 210 567 5055; fax: +1 210 567 5033; e-mail: nathanielsz@uthscsa.edu

Current Opinion in Obstetrics and Gynecology
2008, 20:132–138

Purpose of review
Human epidemiological and animal studies show that many chronic adult conditions have their antecedents in compromised fetal and early postnatal development. Developmental programming is defined as the response by the developing mammalian organism to a specific challenge during a critical time window that alters the trajectory of development with resulting persistent effects on phenotype. Mammals pass more biological milestones before birth than any other time in their lives. Each individual's phenotype is influenced by the developmental environment as much as their genes. A better understanding is required of gene–environment interactions leading to adult disease.

Recent findings
During development, there are critical periods of vulnerability to suboptimal conditions when programming may permanently modify disease susceptibility. Programming involves structural changes in important organs; altered cell number, imbalance in distribution of different cell types within the organ, and altered blood supply or receptor numbers. Compensatory efforts by the fetus may carry a price. Effects of programming may pass across generations by mechanisms that do not necessarily involve structural gene changes. Programming often has different effects in males and females.

Summary
Developmental programming shows that epigenetic factors play major roles in development of phenotype and predisposition to disease in later life.

Keywords
animal studies, developmental programming, human epidemiology

Curr Opin Obstet Gynecol 20:132–138

1040-872X

Introduction

In the last 10–15 years there has been a growth of interest in the concept that many chronic adult conditions have their antecedents in abnormal fetal and early postnatal development. This concept has been termed developmental programming. Developmental programming can be defined as the response by the developing mammalian organism to a specific challenge during a critical time window that alters the trajectory of development qualitatively and/or quantitatively with resulting persistent effects on phenotype.

Developing organisms pass more biological milestones before birth than at any other time in their lives. It should therefore be no surprise that significant alterations in the timing or nature of these developmental steps have consequences in terms of organ function in later life. It also needs to be recognized that the development of each individual's specific phenotype, although based on a specific genotype, is influenced to a varying extent by epigenetic/environmental factors. Although an extreme example, there can be little dispute that the genome of the fetus exposed to repeated and excessive alcohol will function very differently throughout life from the way it would have done in the absence of that exposure. Fetal alcohol syndrome represents the epigenetic effects on the fetal genome of excessive exposure to alcohol during development. Thus it is vitally important to understand the gene–environment interactions that lead to adult disease.

Acceptance and understanding of developmental programming comes from human epidemiological studies and a wealth of carefully controlled animal investigations primarily in rodents and sheep. There are numerous reviews on the exposures, mechanisms and outcomes involved [1–15]. In the early days of the concept of developmental programming several principles rapidly became clear. These are laid out in Table 1 [16]. For this review we will restrict our discussion to six of these principles – 1, 2, 4, 7, 9 and 10 – and focus on controlled animal investigations demonstrating that maternal undernutrition, overnutrition and stress, and fetal hypoxia, are all environmental factors that support the general principles of developmental programming.

Table 1 Ten principles of developmental programming [16]

Principle 1	During development, there are critical periods of vulnerability to suboptimal conditions. Vulnerable periods occur at different times for different tissues. Cells dividing rapidly at the time of exposure are at greatest risk. Risk factors include too much of a normal chemical such as a hormone, critical nutrient or vitamin; deficiency of a normal chemical such as a hormone, critical nutrient or vitamin; abnormal chemicals such as alcohol or nicotine; abnormal physical forces, such as high blood pressure.
Principle 2	Programming has permanent effects that alter responses in later life and can modify susceptibility to disease.
Principle 3	Fetal development is dependent on fetal physical activity. Normal development is dependent on continuing normal activity. Each phase of development provides the required conditions for subsequent development.
Principle 4	Programming may involve structural changes in important organs. The absolute numbers of cells in the organ may increase or decrease; the relative proportions and distribution of different types of cell within the organ may be unbalanced; the normal blood supply to the organ may be compromised; too many or too few hormone receptors may form with a resultant resetting of feedback and other control mechanisms.
Principle 5	The placenta plays a key role in some forms of programming.
Principle 6	Compensation carries a price. In an unfavorable environment, the developing baby makes attempts to compensate for deficiencies. Following compensation, birth weight may be normal or only slightly decreased. However, the compensatory effort carries a price.
Principle 7	Attempts made after birth to reverse the consequences of programming may have their own unwanted consequences. When postnatal conditions prove to be other than those for which the fetus prepared, problems may arise.
Principle 8	Fetal cellular mechanisms often differ from adult processes. Fetuses react differently to suboptimal conditions than do newborn babies or adults.
Principle 9	The effects of programming may pass across generations by mechanisms that do not necessarily involve changes in the genes.
Principle 10	Programming often has different effects in males and females.

Principles 1 and 2

Principle 1 is that there are critical periods of vulnerability to suboptimal conditions that occur at different times for different systems; Principle 2 is that there are permanent effects that alter responses in later life and can modify susceptibility to disease. It is impossible to separate these two principles. The first refers to the timing of exposure and Principle 2 to the outcome resulting from that exposure. Perhaps the best human example comes from the study of individuals who survived the Dutch Hunger Winter of 1944–1945 [17–21]. Children who passed any period of their prenatal development during that time suffered from poor nutrition. Epidemiological studies of these individuals, now over 60 years old, have demonstrated that undernutrition of their mothers at different stages of pregnancy produced different outcomes. For example, undernutrition in the last third of gestation decreased the percentage of the babies who become obese as adults whereas undernutrition during the first two trimesters increased the prevalence of adult obesity [22,23].

The idea that there are critical time windows when developing systems are most vulnerable to challenge, and the fact that these vulnerable periods differ among systems and species, is clearly supported by work in animals. Changes in activity of a given system across development have been clearly demonstrated in numerous models, leading to the suggestion that suboptimal conditions will impact the same system differently depending on the timing of the insult. A well-known example comes from work in several laboratories that provides insights regarding the role of the renin–angiotensin system (RAS) in development of the heart [24–29]. Angiontensin II receptor type 1 (AT1) mRNA levels remained constant across the late gestation period, while receptor type 2 (AT2) mRNA expression was much higher with a dramatic decrease soon after birth [26]. In sheep, AT1 blockade during gestation was shown to have chamber and gestational age-specific effects on AT1 mRNA expression [increased at 95 and 135 days of gestational age (dGA) in the right atrium and the left ventricle at 110 dGA] [26]. Similarly, other investigators have reported that angiontensin II signaling has gestational age-specific effects on fetal heart growth in sheep and pig [25,27]. Sundgren *et al.* [25] have shown that angiontensin II promotes hyperplastic growth during early gestation, whereas Beinlich *et al.* [27] have demonstrated its importance in hypertrophic growth during neonatal life in the pig.

In a now classical study, Barraclough and Gorski [30] demonstrated that when female rats receive a single dose of androgen in the first 5 days of postnatal life, they did not show normal reproductive cycling at puberty. If exposure to androgen occurred 15 days later, near weaning, there was no persistent effect on reproduction. More recent animal studies have focused on poor nutrition in fetal life (for example, isocaloric low-protein diets [31], global nutrient restriction [32,33], and reduced uterine blood flow [34]), maternal stress (in rhesus monkeys [35,36] and pigs [37]) and exposure to various pharmacological agents (such as antenatal glucocorticoids [38–41]). Other studies compare outcomes resulting from insults during fetal life with insults occurring during early postnatal life [42,43].

The study by Barraclough and Gorski [30] also clearly demonstrated the second principle of developmental

programming, namely that there are permanent effects of neonatal androgen exposure on structures in the brain, particularly the hypothalamus, that regulate female reproductive cycle, following exposure at a critical time in development. More recently various well-characterized animal models have shown long-term consequences for the offspring. In rats, guinea-pigs, sheep and humans, fetal growth restriction and reduction in either maternal protein or global caloric intake leads to hypertension [44–50], obesity [10,51–56], diabetes [9,57–61], altered endocrine function [62–67] and mood disorders [68–71]. Finally, in comparing conclusions based on data from different species, it is clear that the trajectory of development of different systems varies between species. The simplest examples are differences between altricial species (born in an immature state and in which much development occurs after birth) and precocial species (born at a more advanced state of maturation). Thus the periods of vulnerability of the developing reproductive system which are postnatal in rodents are generally prenatal in sheep and humans.

Principle 4

Principle 4 states that programming may involve structural changes in important organs. We can say with confidence that a suboptimal developmental environment alters organ growth. The absolute numbers of cells in an organ may increase or decrease as a result of nutrient insufficiency and altered cell growth and division. Organ growth restriction has been demonstrated in models of maternal nutrient restriction [72,73], decrease in uterine blood supply as a result of uterine artery ligation [74] or uterine or umbilical artery embolization [75,76]. In each model the fetal nutrient supply is compromised.

Growth restriction may manifest itself only within certain components of an organ. We have shown that maternal nutrient restriction during the first half of gestation in the sheep induces asymmetric growth restriction [73]. Regardless of the cause, deficient levels of nutrients and oxygen lead to alterations in blood flow to, and vascular development in, the fetal brain, heart, lungs, abdominal viscera and skeletal muscle [77,78]. Maternal low-protein diets given to rats in pregnancy result in a smaller number of blood vessels per unit area in the fetal rat pancreas [79]. This decrease in potential vascular perfusion of the pancreas is likely to limit pancreatic islet function and be one of the major factors in the predisposition of offspring of nutrient-restricted mothers to develop diabetes.

Growth of the fetal kidney has received considerable attention because of its importance both during fetal life and in the transition to an independent postnatal existence. Several studies have investigated aspects of the renal structure following nutritional deficit during pregnancy. In humans, fetal growth restriction is associated with a decrease in kidney size [80,81] and post-mortem glomerulus number [82]. Hughson *et al.* [83] showed a direct relationship between total glomeruli number in adult humans and birth weight. Furthermore, mean glomerulus volume was inversely correlated with glomerulus number. In rodents and sheep a reduction in total caloric food intake [49,84] or total dietary protein [85–87] during pregnancy induced a nephron deficit [88] and an increase in glomerular size [87]. Recently, a maternal diet low in protein has been shown to alter these relationships by changing cell turnover and gene expression at the beginning of metanephrogenesis in rats [89].

Widespread change in receptor populations is a further refinement of the idea that structure is impacted by a suboptimal environment *in utero*. Glucose transport proteins are found in fetal tissues from early in gestation [90–92] and are altered by maternal under nutrition [93]. Gene and protein expression within the fetal kidney, for example, has recently been found to be sensitive to maternal nutrient status in the rat [89,94,95], sheep [96,97•] and the baboon [98–100]. Recent reports from our group have shown that maternal nutrient restriction during the first half of gestation in the sheep induces asymmetric growth restriction [73], alters gene transcription in the fetal heart [101–104], downregulates fetal skeletal-muscle protein synthesis [105], and alters concentrations of amino acids in fetal fluids by mid-gestation [106].

Principle 7

Principle 7 states that when postnatal conditions prove to be other than those for which the fetus prepared, problems may arise. The livers of fetal rats undernourished *in utero* show dramatically altered function and structure [107]. Individual lobules have more cells with phosphoenolpyruvate carboxykinase (PEPCK) activity than fetal livers of rats whose mothers received adequate nutrition. PEPCK is the key gluconeogenic enzyme and this nutrionally induced change indicates the fetal need to increase gluconeogenesis in the face of decreased glucose availability. Forhead and colleagues [108] have shown in the chronically catheterized fetal sheep that an increase in PEPCK is one of the many changes the fetus normally makes in late development to prepare to perform gluconeogenesis postnatally. If the neonate has an imbalance in liver glucose metabolism tending towards increased glucose production, that adaptation will be of value if food shortage is experienced postnatally. This response to adverse prenatal conditions has been called a predictive adaptive response (PAR), indicating its value in helping the offspring survive [109]. However, if the postnatal dietary regimen is adequate – or even

overabundant, as in our overconsumption-orientated society – the PAR is maladaptive and may predispose to obesity.

The idea that it is important to match prenatal development with the postnatal environment has important implications for the management of growth-restricted human neonates. Animal models have a major role to play in understanding effects of altered diet at different times of development with subsequent postnatal changes. Some outcomes of developmental programming can be certainly considered as PARs (such as an increased tendency to gluconeogenesis, which will be beneficial to survival under certain circumstances). However, other outcomes are distinctly maladaptive responses (MARs). Outcomes that could be considered MARs with no apparent value to survival are the decreased muscle mass or numbers of glomeruli that result from maternal nutrient deficiencies and predispose directly and inevitably to suboptimal health in later life.

Several rodent studies have investigated outcomes when neonates that are growth restricted at birth have been fed postnatally to induce catch-up growth [42,110]. As discussed above if the postnatal environment differs from the one in which the fetus developed, the mismatch may lead to later health problems. Ozanne and Hales [42] fed pregnant mice either a 20% protein or an 8% low-protein diet to restrict fetal growth and cross fostered pups at birth so that the offspring of mothers fed on a low-protein diet during pregnancy were reared by normally fed dams, the catch-up group. In the low-protein group offspring of mothers fed the normal protein diet during pregnancy were reared by mothers fed on a low-protein diet. Offspring in the catch-up group showed rapid catch-up growth and died earlier than controls. Interestingly, mice that grew normally before birth but were fed by mothers on the low-protein diet lived 57% longer than the catch-up group, approximately equivalent to a human living 75 rather than 50 years [42].

Principle 9

Principle 9 is that programming may cross generations. The consequences of various challenges to which the developing organism is exposed can be passed transgenerationally from female offspring, challenged during their own development to their own offspring [111]. In the 1990s two independent groups of investigators demonstrated that the F_1 female diabetic offspring of F_0 rats treated with streptozotocin during pregnancy themselves have F_2 offspring with altered glucose and carbohydrate metabolism [112–114].

More recently, Zambrano and colleagues [110] determined whether, when F_0 female rats are exposed to protein restriction during pregnancy and/or lactation, their female pups (the F_1 daughters) deliver offspring (the F_2, or granddaughters and grandsons) with evidence *in vivo* of altered glucose and insulin metabolism. The F_0 rats were fed a normal control 20% casein diet (C) or a restricted diet (R) of 10% casein during pregnancy. After delivery, the mothers received either C or R diet during lactation to provide four sets of offspring – groups CC, RR, CR, and RC – where the first letter represents the diet during pregnancy and the second the diet during lactation. All the female offspring were fed *ad libitum* with C diet after weaning and during their first pregnancy and lactation. As they grew the female offspring of RR and CR mothers had low body weight and food intake with increased sensitivity to insulin during a glucose tolerance test at 110 days of postnatal life. Grandsons of the CR mothers showed evidence of insulin resistance. In contrast, granddaughters of the RC mothers showed evidence of insulin resistance.

Principle 10

Principle 10 is that programming may affect males and females differently. It is fairly well accepted that men are at greater risk for cardiovascular and renal disease than women of similar ages [115–117]. Recent work has clearly shown sex-specific expression of genes that code for proteins involved in drug metabolism and osmoregulation in the murine kidney that may directly contribute to sex effects in renal development or function [118]. Similarly, genes encoding drug and steroid metabolism were found differentially expressed between the sexes in the liver [118], an organ in which gender-specific transcriptional regulation of numerous genes by growth hormone has been described [119–122].

The transgenerational study by Zambrano *et al.* [110] demonstrates that maternal protein restriction adversely impacts glucose and insulin metabolism of male and female second-generation offspring in a manner specific to gender and the developmental time window. There are many other examples now in the literature of differing responses of male and female offspring to a variety of challenges. Recent work in rats has shown gender differences in the programming of the myogenic vasodilatory response to nitric oxide and prostaglandins in the mesenteric vasculature in male offspring following hypoxia during gestation [123]. In another study using radiotelemetric recording methods in conscious rats, raised blood pressure in female but not male offspring of dams fed a diet rich in animal lard has been demonstrated [124].

Our work in sheep has shown that maternal global caloric restriction alters intrarenal immunoreactive AT1, AT2 and renin expression in ways specific to gestational age

and gender [97•]. We have also evaluated the effect of 30% global restriction from 30 to 90 days of gestation in the baboon (term 180 days) on the intrarenal RAS in male and female fetal kidneys at 90 days. Steady-state mRNA and protein were evaluated using the Human Genechip U133A 2.0 or Western blot in six controls fed *ad libitum* (C; three males, three females) and six nutrient-restricted (NR; three males, three females) fetuses. AT1 mRNA was increased (92%) in NR males (NRM) compared with C males (CM), C females (CF), and NR females (NRF). Both diet and the interaction between diet and gender were significant. There was no diet or gender effect on AT2 mRNA expression. Renal AT1 protein expression exhibited both diet and gender effects, with immunoreactivity being increased in NRM compared with all other groups. Conversely, AT2 protein was decreased in NRM compared with CM, CF and NRF, resulting in an AT1/AT2 protein ratio that was increased in NRM compared with CM, CF and NRF. A diet–gender interaction was observed on angiotensin-converting enzyme (ACE) immunoreactivity. Finally, no group differences were found in maternal plasma cortisol concentrations at 90 days. We found that diet-induced alterations in mRNA and protein expression, and the AT1/AT2 protein ratio, occur in male fetuses rather than females and are independent of maternal cortisol levels, leading to the postulate that gender-based sensitivity to nutrient deficit likely reflects differences between trajectories of growth, development and caloric demand in male and female fetuses.

Conclusion

The mounting human epidemiological and controlled animal experimental data clearly demonstrate that adult health is determined by both an individual's genome and the environment in which that genome develops. Whereas there are genetic conditions such as Huntington's chorea and cystic fibrosis that have a dominant and inevitable effect on adult health, the phenotype that emerges as a result of the interaction of epigenetic influences on the genome is critical to good adult health in a much larger segment of the population. Thus understanding the prenatal (and immediate postnatal) influences on adult disease and developing preventive strategies for pregnancies at risk is one of the major challenges of biomedical research and the delivery of obstetric care.

Acknowledgements

We are grateful for the contributions of our colleagues to our own research in this subject area: Laura A. Cox PhD, Jeffrey S. Gilbert PhD, Cun Li MD, Thomas J. McDonald PhD, Natalia E. Schalbritz-Loutsevitch MD PhD and Elena Zambrano PhD. This work was supported in part by NIH grants HD 21350 (PWN/MJN) and INBRE P20 RR16474-04 (SPF).

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 196–197).

1 Myatt L. Placental adaptive responses and fetal programming. J Physiol 2006; 572:25–30.

2 Maloney CA, Rees WD. Gene-nutrient interactions during fetal development. Reproduction 2005; 130:401–410.

3 Foster DL, Jackson LM, Padmanabhan V. Programming of GnRH feedback controls timing puberty and adult reproductive activity. Mol Cell Endocrinol 2006; 254–255:109–119.

4 Fowden AL, Sibley C, Reik W, *et al.* Imprinted genes, placental development and fetal growth. Horm Res 2006; 65 (suppl 3):50–58.

5 Symonds ME, Stephenson T, Gardner DS, *et al.* Long-term effects of nutritional programming of the embryo and fetus: mechanisms and critical windows. Reprod Fertil Dev 2007; 19:53–63.

6 Phillips DI, Jones A, Goulden PA. Birth weight, stress, and the metabolic syndrome in adult life. Ann N Y Acad Sci 2006; 1083:28–36.

7 Meaney MJ. Environmental programming of phenotypic diversity in female reproductive strategies. Adv Genet 2007; 59:173–215.

8 Gardner DS, Bell RC, Symonds ME. Fetal mechanisms that lead to later hypertension. Curr Drug Targets 2007; 8:894–905.

9 Devaskar SU, Thamotharan M. Metabolic programming in the pathogenesis of insulin resistance. Rev Endocr Metab Disord 2007; 8:105–113.

10 Bouret SG, Simerly RB. Developmental programming of hypothalamic feeding circuits. Clin Genet 2006; 70:295–301.

11 Nathanielsz PW. Animal models that elucidate basic principles of the developmental origins of adult diseases. Inst Laboratory Anim Res J 2006; 47:73–82.

12 Sloboda DM, Challis JR, Moss TJ, *et al.* Synthetic glucocorticoids: antenatal administration and long-term implications. Curr Pharm Des 2005; 11:1459–1472.

13 McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. Physiol Rev 2005; 85:571–633.

14 Davies MJ. Fetal programming: the perspective of single and twin pregnancies. Reprod Fertil Dev 2005; 17:379–386.

15 Gilbert JS, Cox LA, Mitchell G, *et al.* Nutrient-restricted fetus and the cardiorenal connection in hypertensive offspring. Expert Rev Cardiovasc Ther 2006; 4:227–237.

16 Nathanielsz PW. Life in the womb: the origin of health and disease. Ithaca, New York: Promethean Press; 1999.

17 Lumey LH. Decreased birthweights in infants after maternal in utero exposure to the Dutch famine of 1944–1945. Paediatr Perinat Epidemiol 1992; 6:240–253.

18 Lumey LH, Ravelli AC, Wiessing LG, *et al.* The Dutch famine birth cohort study: design, validation of exposure, and selected characteristics of subjects after 43 years follow-up. Paediatr Perinat Epidemiol 1993; 7:354–367.

19 Neugebauer R, Hoek HW, Susser E. Prenatal exposure to wartime famine and development of antisocial personality disorder in early adulthood. J Am Med Assoc 1999; 282:455–462.

20 Painter RC, Roseboom TJ, Bleker OP. Prenatal exposure to the Dutch famine and disease in later life: an overview. Reprod Toxicol 2005; 20:345–352.

21 Smith CA. Effects of maternal undernutrition upon the newborn infant in Holland (1944–1945). J Pediatr 1947; 3:229–243.

22 de Rooij SR, Painter RC, Phillips DI, *et al.* Impaired insulin secretion after prenatal exposure to the Dutch famine. Diabetes Care 2006; 29:1897–1901.

23 Brown AS, Susser ES, Lin SP, *et al.* Increased risk of affective disorders in males after second trimester prenatal exposure to the Dutch hunger winter of 1944–45. Br J Psychiatry 1995; 166:601–606.

24 Segar JL, Dalshaug GB, Bedell KA, *et al.* Angiotensin II in cardiac pressure-overload hypertrophy in fetal sheep. Am J Physiol Regul Integr Comp Physiol 2001; 281:R2037–R2047.

25 Sundgren NC, Giraud GD, Stork PJ, *et al.* Angiotensin II stimulates hyperplasia but not hypertrophy in immature ovine cardiomyocytes. J Physiol 2003; 548:881–891.

26 Samyn ME, Petershack JA, Bedell KA, *et al.* Ontogeny and regulation of cardiac angiotensin types 1 and 2 receptors during fetal life in sheep. Pediatr Res 1998; 44:323–329.

27 Beinlich CJ, Rissinger CJ, Morgan HE. Mechanisms of rapid growth in the neonatal pig heart. J Mol Cell Cardiol 1995; 27:273–281.

28 Beinlich CJ, White GJ, Baker KM, *et al.* Angiotensin II and left ventricular growth in newborn pig heart. J Mol Cell Cardiol 1991; 23:1031–1038.

29 Beinlich CJ, Morgan HE. Control of growth in neonatal pig hearts. Mol Cell Biochem 1993; 119:3–9.

30 Barraclough CA, Gorski RA. Evidence that the hypothalamus is responsible for androgen-induced sterility in the female rat. Endocrinology 1961; 68:68–79.

31 Ozanne SE, Wang CL, Coleman N, *et al.* Altered muscle insulin sensitivity in the male offspring of protein-malnourished rats. Am J Physiol Endocrinol Metab 1996; 271:E1128–E1134.

32 Blondeau B, Garofano A, Czernichow P, *et al.* Age-dependent inability of the endocrine pancreas to adapt to pregnancy: a long-term consequence of perinatal malnutrition in the rat. Endocrinology 1999; 140:4208–4213.

33 Garofano A, Czernichow P, Breant B. Effect of ageing on beta-cell mass and function in rats malnourished during the perinatal period. Diabetologia 1999; 42:711–718.

34 Simmons RA, Templeton LJ, Gertz SJ. Intrauterine growth retardation leads to the development of type 2 diabetes in the rat. Diabetes 2001; 50:2279–2286.

35 Clarke AS. Prenatal stress has long-term effects on behavioral responses to stress in juvenile rhesus monkeys. Dev Psychobiol 1993; 26:293–304.

36 Schneider ML, Suomi SJ. Neurobehavioral assessment in rhesus monkey neonates (*Macaca mulatta*): developmental changes, behavioral stability, and early experience. Infant Behav Dev 1992; 15:155–177.

37 Kanitz E, Otten W, Tuchscherer M. Changes in endocrine and neurochemical profiles in neonatal pigs prenatally exposed to increased maternal cortisol. J Endocrinol 2006; 191:207–220.

38 Dodic M, May CN, Wintour EM, *et al.* An early prenatal exposure to excess glucocorticoid leads to hypertensive offspring in sheep. Clin Sci 1998; 94:149–155.

39 Dodic M, Abouantoun T, O'Connor A, *et al.* Programming effects of short prenatal exposure to dexamethasone in sheep. Hypertension 2002; 40:729–734.

40 Derks JB, Giussani DA, Jenkins SL, *et al.* A comparative study of cardiovascular, endocrine and behavioural effects of betamethasone and dexamethasone administration to fetal sheep. J Physiol 1997; 449:217–226.

41 Glover V, Miles R, Matta S, *et al.* Glucocorticoid exposure in preterm babies predicts saliva cortisol response to immunization at 4 months. Pediatr Res 2005; 58:1233–1237.

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

43 Zambrano E, Rodriguez-Gonzalez GL, Guzman C, *et al.* A maternal low protein diet during pregnancy and lactation in the rat impairs male reproductive development. J Physiol 2005; 563:275–284.

44 Jackson AA, Dunn RL, Marchand MC, *et al.* Increased systolic blood pressure in rats induced by a maternal low-protein diet is reversed by dietary supplementation with glycine. Clin Sci 2003; 103:633–639.

45 Langley-Evans SC, Jackson AA. Captopril normalises systolic blood pressure in rats with hypertension induced by fetal exposure to maternal low protein diets. Comp Biochem Physiol 1995; 110:223–228.

46 Brawley L, Itoh S, Torrens C, *et al.* Dietary protein restriction in pregnancy induces hypertension and vascular defects in rat male offspring. Pediatr Res 2003; 54:83–90.

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

48 Kind KL, Clifton PM, Grant PA, *et al.* Effect of maternal feed restriction during pregnancy on glucose tolerance in the adult guinea pig. Am J Physiol Regul Integr Comp Physiol 2003; 284:R140–R152.

49 Gilbert JS, Lang AL, Grant AR, *et al.* Maternal nutrient restriction in sheep: hypertension and decreased nephron number in offspring at 9 months of age. J Physiol 2005; 565:137–147.

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

51 Taylor PD, Poston L. Developmental programming of obesity in mammals. Exp Physiol 2007; 92:287–298.

52 Choi GY, Tosh DN, Garg A, *et al.* Gender-specific programmed hepatic lipid dysregulation in intrauterine growth-restricted offspring. Am J Obstet Gynecol 2007; 196:477.e1–477.e7.

53 Samuelsson AM, Matthews PA, Argenton M, *et al.* Diet-induced obesity in female mice leads to offspring hyperphagia, adiposity, hypertension, and insulin resistance. A novel murine model of developmental programming. Hypertension 2008; 51:383–392.

54 Budge H, Gnanalingham MG, Gardner DS, *et al.* Maternal nutritional programming of fetal adipose tissue development: long-term consequences for later obesity. Birth Defects Res C Embryo Today 2005; 75:193–199.

55 Gnanalingham MG, Mostyn A, Symonds ME, *et al.* Ontogeny and nutritional programming of adiposity in sheep: potential role of glucocorticoid action and uncoupling protein-2. Am J Physiol Regul Integr Comp Physiol 2005; 289:R1407–R1415.

56 Breier BH, Vickers MH, Ikenasio BA, *et al.* Fetal programming of appetite and obesity. Mol Cell Endocrinol 2001; 185:73–79.

57 Simmons RA. Developmental origins of diabetes: the role of epigenetic mechanisms. Curr Opin Endocrinol Diabetes Obes 2007; 14:13–16.

58 Reusens B, Remacle C. Programming of the endocrine pancreas by the early nutritional environment. Int J Biochem Cell Biol 2006; 38:913–922.

59 Schwitzgebel VM. Programming of the pancreas. Mol Cell Endocrinol 2001; 185:99–108.

60 Hill DJ, Duvillie B. Pancreatic development and adult diabetes. Pediatr Res 2000; 48:269–274.

61 Holness MJ, Langdown ML, Sugden MC. Early-life programming of susceptibility to dysregulation of glucose metabolism and the development of Type 2 diabetes mellitus. Biochem J 2000; 349:657–665.

62 Hyatt MA, Budge H, Walker D, *et al.* Ontogeny and nutritional programming of the hepatic growth hormone-insulin-like growth factor-prolactin axis in the sheep. Endocrinology 2007; 148:4754–4760.

63 Chadio SE, Kotsampasi B, Papadomichelakis G, *et al.* Impact of maternal undernutrition on the hypothalamic-pituitary-adrenal axis responsiveness in sheep at different ages postnatal. J Endocrinol 2007; 192:495–503.

64 Wallace J, Bourke D, Da Silva SP, Aitken R. Nutrient partitioning during adolescent pregnancy. Reproduction 2001; 122:347–357.

65 Lingas RI, Matthews SG. A short period of maternal nutrient restriction in late gestation modifies pituitary-adrenal function in adult guinea pig offspring. Neuroendocrinology 2001; 73:302–311.

66 Hoet JJ, Ozanne S, Reusens B. Influences of pre and postnatal nutritional exposures on vascular/endocrine systems in animals. Environ Health Perspect 2000; 108 (suppl 3):563–568.

67 Lingas R, Dean F, Matthews SG. Maternal nutrient restriction (48 h) modifies brain corticosteroid receptor expression and endocrine function in the fetal guinea pig. Brain Res 1999; 846:236–242.

68 Costello EJ, Worthman C, Erkanli A, *et al.* Prediction from low birth weight to female adolescent depression: a test of competing hypotheses. Arch Gen Psychiatry 2007; 64:338–344.

69 Flu RB. Impact of gestational distress and growth retardation on emotional problems in offspring. Acta Psychiatr Scand 2007; 116:154–155.

70 Berle JO, Mykletun A, Daltveit AK, *et al.* Outcomes in adulthood for children with foetal growth retardation. A linkage study from the Nord-Trondelag Health Study (HUNT) and the Medical Birth Registry of Norway. Acta Psychiatr Scand 2006; 113:501–509.

71 Gale CR, Martyn CN. Birth weight and later risk of depression in a national birth cohort. Br J Psychiatry 2004; 184:28–33.

72 Clarke L, Heasman L, Juniper DT, *et al.* Maternal nutrition in early mid-gestation and placental size in sheep. Br J Nutr 2001; 79:359–364.

73 Vonnahme KA, Hess BW, Hansen TR, *et al.* Maternal undernutrition from early- to mid-gestation leads to growth retardation, cardiac ventricular hypertrophy, and increased liver weight in the fetal sheep. Biol Reprod 2003; 69:133–140.

74 Wlodek ME, Westcott KT, O'Dowd R, *et al.* Uteroplacental restriction in the rat impairs fetal growth in association with alterations in placental growth factors including PTHrP. Am J Physiol Regul Integr Comp Physiol 2005; 288:R1620–R1627.

75 Block BS, Schlafer DH, Wentworth RA, *et al.* Intrauterine growth retardation and the circulatory responses to acute hypoxemia in fetal sheep. Am J Obstet Gynecol 1989; 161:1576–1579.

76 Gagnon R, Challis J, Johnston L, *et al.* Fetal endocrine responses to chronic placental embolization in the late-gestation ovine fetus. Am J Obstet Gynecol 1994; 170:929–938.

77 Kempley ST, Gamsu HR, Vyas S, *et al.* Effects of intrauterine growth retardation on postnatal visceral and cerebral blood flow velocity. Arch Dis Child 1991; 66:1115–1118.

78 McMillen IC, Adams MB, Ross JT, *et al.* Fetal growth restriction: adaptations and consequences. Reproduction 2001; 122:195–204.

79 Snoeck A, Remacle C, Reusens B, *et al.* Effect of a low protein diet during pregnancy on the fetal rat endocrine pancreas. Biol Neonate 1990; 57:107–118.

80 Silver LE, Decamps PJ, Korst LM, *et al.* Intrauterine growth restriction is accompanied by decreased renal volume in the human fetus. Am J Obstet Gynecol 2003; 188:1320–1325.

81 Latini G, De Mitri B, Del Vecchio A, *et al.* Foetal growth of kidneys, liver and spleen in intrauterine growth restriction: ''programming'' causing ''metabolic syndrome'' in adult age. Acta Paediatr 2004; 93:1635–1639.

82 Hinchliffe SA, Lynch MR, Sargent PH, *et al.* The effect of intrauterine growth retardation on the development of renal nephrons. Br J Obstet Gynaecol 1992; 99:296–301.

83 Hughson M, Farris AB III, Douglas-Denton R, *et al.* Glomerular number and size in autopsy kidneys: the relationship to birth weight. Kidney Int 2003; 63:2113–2122.

84 Woodall SM, Johnston BM, Breier BH, *et al.* Chronic maternal undernutrition in the rat leads to delayed postnatal growth and elevated blood pressure of offspring. Pediatr Res 1996; 40:438–443.

85 Langley-Evans SC, Welham SJ, Jackson AA. Fetal exposure to a maternal low protein diet impairs nephrogenesis and promotes hypertension in the rat. Life Sci 1999; 64:965–974.

86 Woods LL, Weeks DA, Rasch R. Programming of adult blood pressure by maternal protein restriction: role of nephrogenesis. Kidney Int 2004; 65:1339–1348.

87 Woods LL, Ingelfinger JR, Nyengaard JR, *et al.* Maternal protein restriction suppresses the newborn renin-angiotensin system and programs adult hypertension in rats. Pediatr Res 2001; 49:460–467.

88 Merlet-Benichou C, Gilbert T, Muffat-Joly M, *et al.* Intrauterine growth retardation leads to a permanent nephron deficit in the rat. Pediatr Nephrol 1994; 8:175–180.

89 Welham SJ, Riley PR, Wade A, *et al.* Maternal diet programs embryonic kidney gene expression. Physiol Genomics 2005; 22:48–56.

90 Sadiq HF, Das UG, Tracy TF, *et al.* Intra-uterine growth restriction differentially regulates perinatal brain and skeletal muscle glucose transporters. Brain Res 1999; 823:96–103.

91 Schroeder RE, Doria-Medina CL, Das UG, *et al.* Effect of maternal diabetes upon fetal rat myocardial and skeletal muscle glucose transporters. Pediatr Res 1997; 41:11–19.

92 Simmons RA, Flozak AS, Ogata ES. The effect of insulin and insulin-like growth factor-I on glucose transport in normal and small for gestational age fetal rats. Endocrinology 1993; 133:1361–1368.

93 Dandrea J, Wilson V, Gopalakrishnan G, *et al.* Maternal nutritional manipulation of placental growth and glucose transporter 1 (GLUT-1) abundance in sheep. Reproduction 2001; 122:793–800.

94 Vehaskari VM, Stewart T, Lafont D, *et al.* Kidney angiotensin and angiotensin receptor expression in prenatally programmed hypertension. Am J Physiol Renal Physiol 2004; 287:F262–F267.

95 Sahajpal V, Ashton N. Renal function and angiotensin AT1 receptor expression in young rats following intrauterine exposure to a maternal low-protein diet. Clin Sci (Lond) 2003; 104:607–614.

96 Whorwood CB, Firth KM, Budge H, *et al.* Maternal undernutrition during early to midgestation programs tissue-specific alterations in the expression of the glucocorticoid receptor, 11β-hydroxysteroid dehydrogenase isoforms, and type-1 angiotensin II receptor in neonatal sheep. Endocrinology 2001; 142:2854–2864.

97 • Gilbert JS, Ford SP, Lang AL, *et al.* Nutrient restriction impairs nephrogenesis in a gender-specific manner in the ovine fetus. Pediatr Res 2007; 61:42–47.
This study provides a good example of gender-specific effects and Principle 10.

98 Shade RE, Cox L, Schlabritz-Loutsevitch N, *et al.* Maternal nutrient restriction (NR) influences fetal renal genes related to nephrogenesis. J Soc Gynecol Invest 2005; 12:121A–122A.

99 Cox LA, Nijland MJ, Gilbert JS, *et al.* Effect of thirty percentage maternal nutrient restriction from 0.16 to 0.5 gestation on fetal baboon kidney gene expression. J Physiol 2006; 572:67–85.

100 Nijland MJ, Schlabritz-Loutsevitch NE, Hubbard GB, *et al.* Nonhuman primate fetal kidney transcriptome analysis indicates mammalian target of rapamycin (mTOR) is a central nutrient-responsive pathway. J Physiol 2007; 579:643–656.

101 Han HC, Austin KJ, Nathanielsz PW, *et al.* Maternal nutrient restriction alters gene expression in the ovine fetal heart. J Physiol 2004; 558:111–121.

102 Gilbert JS, Lang AL, Nijland MJ. Maternal nutrient restriction and the fetal left ventricle: decreased angiotensin receptor expression. Reprod Biol Endocrinol 2005; 3:27.e1–27.e10.

103 Dong F, Ford SP, Fang CX, *et al.* Maternal nutrient restriction during early to mid gestation up-regulates cardiac insulin-like growth factor (IGF) receptors associated with enlarged ventricular size in fetal sheep. Growth Horm IGF Res 2005; 15:291–299.

104 Dong F, Ford SP, Nijland MJ, *et al.* Influence of maternal undernutrition and overfeeding on cardiac ciliary neurotrophic factor receptor and ventricular size in fetal sheep. J Nutr Biochem 2007 [epub ahead of print].

105 Zhu MJ, Ford SP, Nathanielsz PW, *et al.* Effect of maternal nutrient restriction in sheep on the development of fetal skeletal muscle. Biol Reprod 2004; 71:1968–1973.

106 Kwon H, Ford SP, Bazer FW, *et al.* Maternal nutrient restriction reduces concentrations of amino acids and polyamines in ovine maternal and fetal plasma and fetal fluids. Biol Reprod 2004; 71:901–908.

107 Hales CN, Desai M, Ozanne SE, *et al.* Fishing in the stream of diabetes: from measuring insulin to the control of fetal organogenesis. Biochem Soc Trans 1996; 24:341–350.

108 Forhead AJ, Poore KR, Mapstone J, *et al.* Developmental regulation of hepatic and renal gluconeogenic enzymes by thyroid hormones in fetal sheep during late gestation. J Physiol 2003; 548:941–947.

109 Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. Science 2004; 305:1733–1736.

110 Zambrano E, Martinez-Samayoa PM, Bautista CJ, *et al.* Sex differences in transgenerational alterations of growth and metabolism in progeny (F2) of female offspring (F1) of rats fed a low protein diet during pregnancy and lactation. J Physiol 2005; 566:225–236.

111 Gluckman PD, Hanson MA, Beedle AS. Nongenomic transgenerational inheritance of disease risk. Bioessays 2007; 29:145–154.

112 Holemans K, Aerts L, Van Assche FA. Evidence for an insulin resistance in the adult offspring of pregnant streptozotocin-diabetic rats. Diabetologia 1991; 34:81–85.

113 Aerts L. Maternal diabetes during pregnancy: consequences for the offspring. Diabetes/Metabolism Rev 1990; 6:147–167.

114 Oh W, Gelardi NL, Cha CJM. The cross-generation effect of neonatal macrosomia in rat pups of streptozotocin-induced diabetes. Pediatr Res 1991; 29:606–610.

115 Jungers P, Chauveau P, Descamps-Latscha B, *et al.* Age and gender-related incidence of chronic renal failure in a French urban area: a prospective epidemiologic study. Nephrol Dial Transplant 1996; 11:1542–1546.

116 Hannedouche T, Chauveau P, Kalou F, *et al.* Factors affecting progression in advanced chronic renal failure. Clin Nephrol 1993; 39:312–320.

117 Miller JA, Anacta LA, Cattran DC. Impact of gender on the renal response to angiotensin II. Kidney Int 1999; 55:278–285.

118 Rinn JL, Rozowsky JS, Laurenzi IJ, *et al.* Major molecular differences between mammalian sexes are involved in drug metabolism and renal function. Dev Cell 2004; 6:791–800.

119 Ahluwalia A, Clodfelter KH, Waxman DJ. Sexual dimorphism of rat liver gene expression: regulatory role of growth hormone revealed by deoxyribonucleic Acid microarray analysis. Mol Endocrinol 2004; 18:747–760.

120 Wiwi CA, Gupte M, Waxman DJ. Sexually dimorphic P450 gene expression in liver-specific hepatocyte nuclear factor 4alpha-deficient mice. Mol Endocrinol 2004; 18:1975–1987.

121 Udy GB, Towers RP, Snell RG, *et al.* Requirement of STAT5b for sexual dimorphism of body growth rates and liver gene expression. Proc Nat Acad Sci USA 1997; 94:7239–7244.

122 Teglund S, McKay C, Schuetz E, *et al.* Stat5a and Stat5b proteins have essential and nonessential, or redundant, roles in cytokine responses. Cell 1998; 93:841–850.

123 Hemmings DG, Williams SJ, Davidge ST. Increased myogenic tone in 7-month-old adult male but not female offspring from rat dams exposed to hypoxia during pregnancy. Am J Physiol Heart Circ Physiol 2005; 289:H674–H682.

124 Khan I, Dekou V, Hanson M, *et al.* Predictive adaptive responses to maternal high-fat diet prevent endothelial dysfunction but not hypertension in adult rat offspring. Circulation 2004; 110:1097–1102.