

REVIEW

The intergenerational effects of fetal programming: non-genomic mechanisms for the inheritance of low birth weight and cardiovascular risk

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Abstract

Many epidemiological studies in diverse populations have demonstrated a link between low birth weight and subsequent disease. This evidence has given rise to the fetal origins hypothesis, which suggests that exposure of the fetus to an adverse environment *in utero* leads to permanent programming of tissue function and a risk of cardiovascular disease. An alternative hypothesis is that low birth weight and adult cardiovascular disease are independent features of a genetic predisposition to cardiovascular

disease. This review describes evidence that the programming phenomenon may not be limited to the first generation offspring. Results of human and animal studies identify intergenerational programmed effects on both birth weight and cardiovascular disease. This may represent a mechanism for the non-genetic inheritance of a predisposition to low birth weight and adverse cardiovascular risk across a number of generations.

Journal of Endocrinology (2004) **180**, 1–16

Introduction: the early life origins of disease

Many epidemiological studies in distinct populations in the UK and the rest of the world have demonstrated an association between low birth weight and the subsequent development of hypertension, insulin resistance, type 2 diabetes and cardiovascular disease (Barker 1998). This association appears to be independent of classic lifestyle risk factors such as smoking, adult weight, social class, alcohol and lack of exercise, which are additive to the effect (Barker *et al.* 1993). Importantly, the association holds for the full range of birth weights, including those within the normal range. In addition, a number of studies have suggested that faster postnatal catch-up growth may also be predictive of later risk of cardiovascular disease (Barker *et al.* 1993, Bavdekar *et al.* 1999, Eriksson *et al.* 1999, Forsen *et al.* 2000, Law *et al.* 2002). ‘Fetal programming’ has been proposed as the mechanism underlying this association between low birth weight, childhood growth and subsequent disease. The fetal programming hypothesis proposes that a stimulus or insult acting during critical periods of growth and development may permanently alter tissue structure and function. Indeed, evidence from both human and animal studies (Langley-Evans *et al.* 1996, Barker 1998, Nyirenda *et al.* 1998, Doyle *et al.* 2000)

suggests that many diseases of adult life can be induced by manipulating the environmental experience of the fetus.

The relative importance of genetic and environmental factors in this phenomenon remains unknown. Two major environmental hypotheses have been proposed to explain the mechanism by which low birth weight is associated with adult disease: fetal undernutrition (Barker & Osmond 1986) and overexposure of the fetus to glucocorticoids (Edwards *et al.* 1993). A third hypothesis suggests that genetic factors may lead to both low birth weight and subsequent risk of cardiovascular disease; indeed, genetic loci have recently been described which may link smallness at birth with adult disease (Dunger *et al.* 1998, Hattersley *et al.* 1998).

A somewhat polarised debate has ensued concerning whether the mechanisms of the low birth weight/adult disease associations are programmed/environmental or genetic. As with most nature vs nurture arguments, the answer is probably a mixture of the two. To add to this complexity, however, there is evidence that what appears to be inherited, and implicitly ‘genetic’, may in fact represent a perpetuation of a programming influence through several generations. There is a well-recognised ‘intergenerational cycle of growth failure’ in the developing world – young girls who grow poorly become stunted

women and are more likely to give birth to low birth weight babies. If these infants are girls, they are likely to continue the cycle by being stunted in adulthood and so on (Ramakrishnan *et al.* 1999). Could this apparent intergenerational effect on fetal growth also be important in the developed world? Moreover, could such an effect contribute to adult cardiovascular disease in Westernised societies?

Intergenerational influences

In 1986, Emanuel defined intergenerational influences as 'those factors, conditions, exposures and environments experienced by one generation that relate to the health, growth and development of the next generation' (Emanuel 1986). Epidemiological studies have suggested that there may be intergenerational effects on birth weight (Ounsted & Ounsted 1968, Johnstone & Inglis 1974, Klebanoff *et al.* 1984, Emanuel *et al.* 1992, Hennessy & Alberman 1998, Collins *et al.* 2002). If low birth weight is associated with increased cardiovascular risk, this could lead to the 'inheritance' of a predisposition to low birth weight and adverse cardiovascular risk across a number of generations (Fig. 1).

Potential explanations for intergenerational effects include: (i) that genetic attributes may manifest themselves similarly in mother and offspring; (ii) that adverse extrinsic environmental conditions may persist across generations; and (iii) that adverse *in utero* experiences may permanently affect maternal growth and development, altering her metabolism in such a way as to provide an adverse environment for her fetus. This last hypothesis suggests a mechanism by which programming effects could be self-perpetuating through several generations.

This review will examine the evidence for intergenerational effects on birth weight and adult disease, and whether non-genomic mechanisms may operate to produce programming effects across a number of generations.

Intergenerational effects on birth weight

Studies in a number of different populations have demonstrated that offspring birth weight is related to maternal birth weight (Ounsted & Ounsted 1968, Johnstone & Inglis 1974, Klebanoff *et al.* 1984, 1989, 1997, Carr-Hill *et al.* 1987, Emanuel *et al.* 1992, 1999, Collins *et al.* 2002), a relationship which appears to depend upon reduced intrauterine growth rather than reduced duration of gestation (Klebanoff *et al.* 1984, 1997). In 1968, Ounsted published data from a cohort of growth-retarded and growth-accelerated infants taken from the British Perinatal Mortality survey of 1958 and suggested a matrilineal pattern of birth weight inheritance (Ounsted & Ounsted 1968). However, the study was too small to exclude a

major contribution of the father to offspring birth weight. Subsequently, extensive study of the 1958 birth cohort from the British National Child Development Study showed a direct association between parental and offspring birth weight (Alberman *et al.* 1992, Emanuel *et al.* 1992, Hennessy & Alberman 1998), and assessment of grand-parental data in these and other studies has also provided evidence for a matrilineal multigenerational effect on birth weight (Emanuel *et al.* 1992, Klebanoff *et al.* 1997). Although there is a significant relationship between paternal and offspring birth weight (Emanuel *et al.* 1992, Klebanoff *et al.* 1998, Magnus *et al.* 2001), this association is not as strong as that for maternal birth weight (Alberman *et al.* 1992, Emanuel *et al.* 1992, Coutinho *et al.* 1997, Klebanoff *et al.* 1998).

Intergenerational effects on birth weight are also seen in the developing world. Prospective studies in rural Guatemala found a clear relationship between maternal and offspring birth weight, with an effect nearly twice that seen in developed countries (Ramakrishnan *et al.* 1999).

In addition, secular trends in birth weight may be mediated by intergenerational factors. Studies in the US have identified differing intergenerational birth weight effects among African-American and white populations in Illinois depending on place of birth (Collins *et al.* 2002), suggesting that environmental factors may be influencing the secular trends in birth weight in populations with the same racial background.

Intergenerational effects on cardiovascular risk factors

The link between low birth weight and adult cardiovascular risk could be confounded if both low birth weight and cardiovascular risk were inherited together. If this were the case, then we might expect both parents to have an equal influence on the inheritance of birth weight and later cardiovascular disease. A number of recent studies have demonstrated relationships between parental risk of cardiovascular disease and offspring birth weight (Davey Smith *et al.* 1997, 2000a,b, Smith *et al.* 2001, Lawlor *et al.* 2003a,b). Although not a universal finding (Kinra *et al.* 2003), there is evidence in these studies that parental influence is not equal such that the association of maternal cardiovascular risk with offspring birth weight and cardiovascular risk is stronger than that of the father (Davey Smith *et al.* 1997, Kuznetsova *et al.* 2003).

Considering individual cardiovascular risk factors, there is a well-documented relationship between parental and offspring blood pressure (Watt *et al.* 1991, Walker *et al.* 1998) (Fig. 2). There is also evidence that the inheritance of low birth weight and hypertension may be linked. Mothers with higher blood pressure in later life have been shown to deliver smaller babies, a relationship that confounds that which is found between low birth weight and

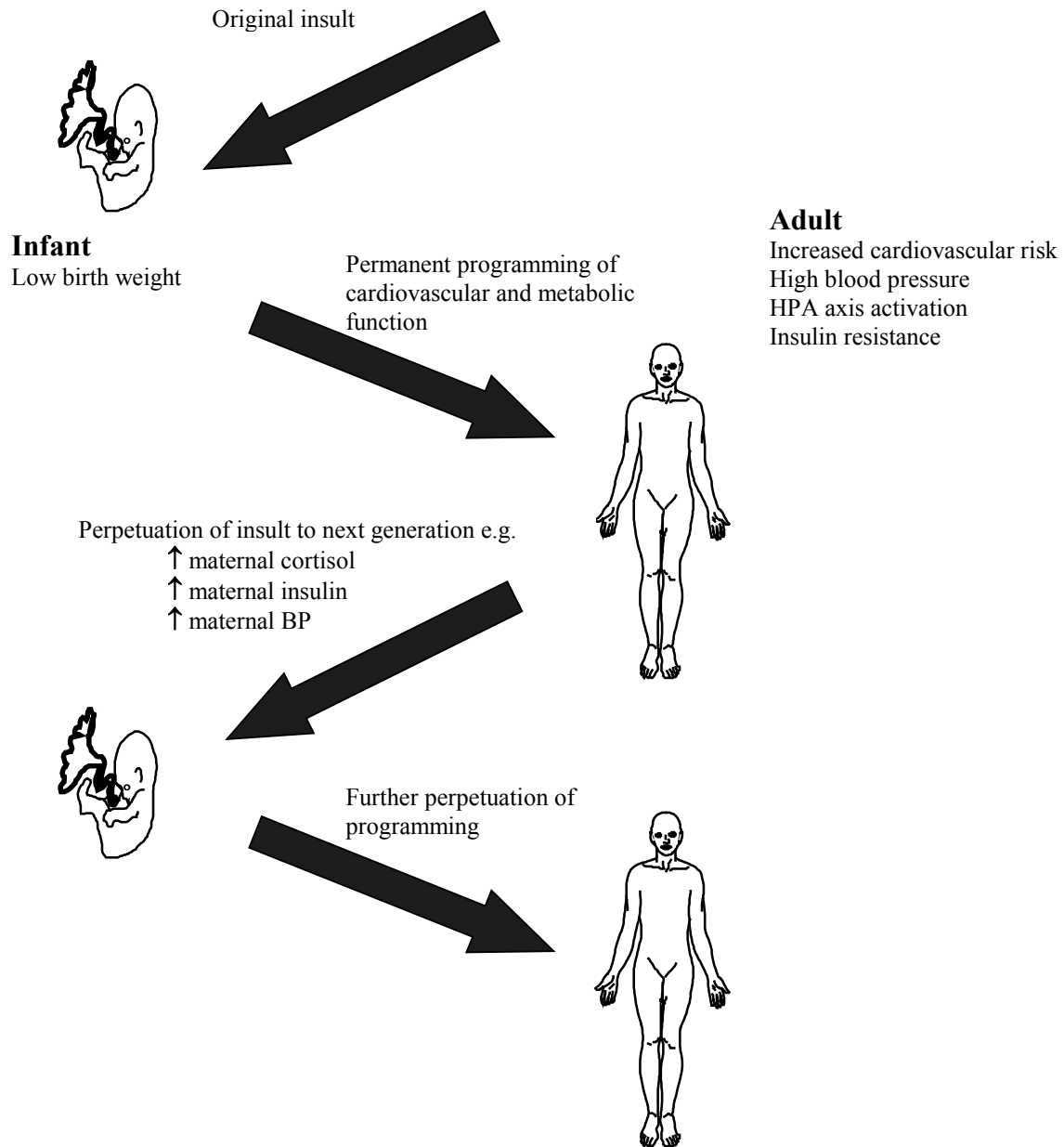


Figure 1 Proposed model for intergenerational programming of birth weight and cardiovascular risk. Exposure of the mother to an adverse environment results in a developmental signal to the F1 offspring, resulting in physiological changes or 'programming'. These changes, with or without continuing environmental stress, lead to a developmental signal for the F2 generation, and thus a cycle of intergenerational programming.

adult hypertension (Walker *et al.* 1998, Lawlor *et al.* 2002) (Fig. 2). Women who were small for gestational age are at increased risk of developing hypertension during pregnancy (Klebanoff *et al.* 1999), and hypertension during pregnancy predicts the delivery of low birth weight babies (Misra 1996, Ferrer *et al.* 2000, Brown *et al.* 2001, Buchbinder *et al.* 2002). Additionally, there is a continu-

ous inverse association between fetal growth and maternal blood pressure across the range seen in normal pregnancy; higher maternal diastolic blood pressure during later pregnancy is predictive of lower offspring birth weight (Churchill *et al.* 1997). However, although paternal blood pressure is associated with offspring blood pressure, it does not reliably predict offspring birth weight

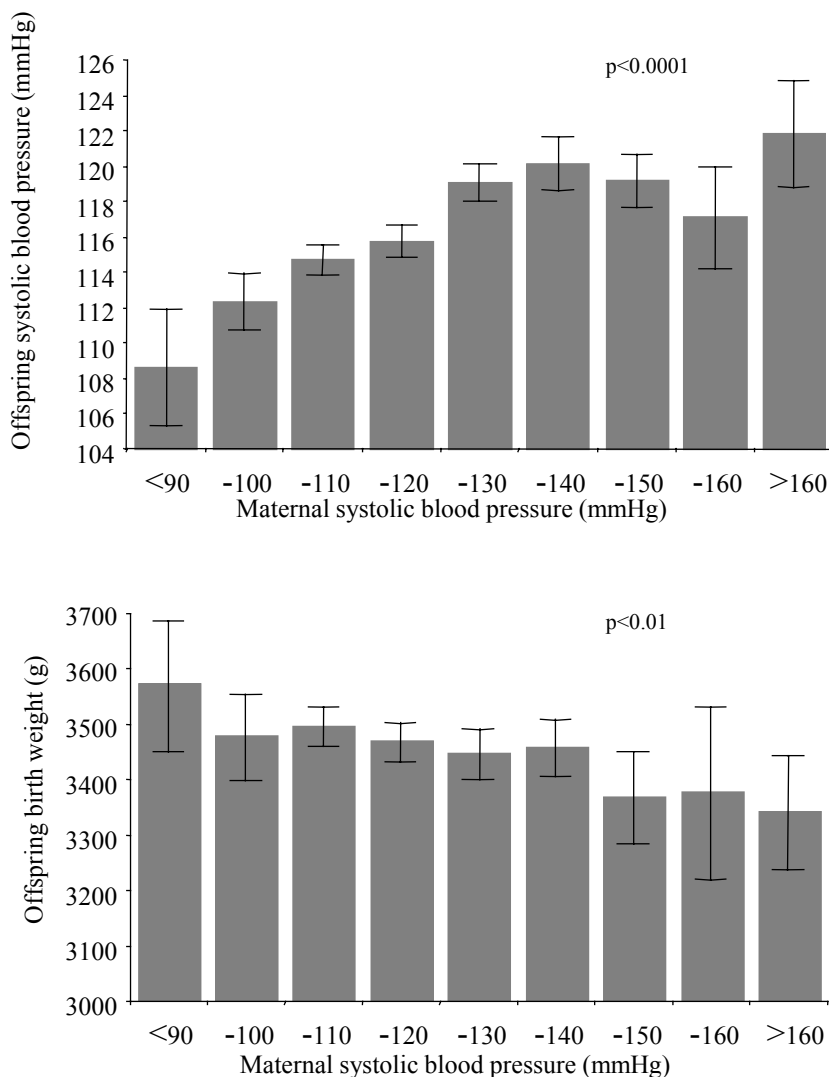


Figure 2 Offspring blood pressure is related to maternal blood pressure. Higher maternal blood pressure is associated with higher offspring blood pressure and lower birth weight in a study of 452 young adults. These relationships confound that which is found between low birth weight and adult hypertension in the offspring. (Adapted from Walker *et al.* 1998.)

(Walker *et al.* 1998). Furthermore, lower maternal but not paternal birth weight is related to higher offspring blood pressure, an association which is largely independent of the relationship between maternal and offspring birth weight (Barker *et al.* 2000).

There have been many studies of the association of parental diabetes with offspring diabetes risk (Alcolado & Alcolado 1991, Thomas *et al.* 1994, Klein *et al.* 1996, Viswanathan *et al.* 1996, Karter *et al.* 1999, Dabelea *et al.* 2000a, Lindsay *et al.* 2000, Meigs *et al.* 2000, Yajnik *et al.* 2001). Studies of women in the US Nurses study, and those from Pima Native American populations have dem-

onstrated that the offspring of mothers with diabetes during pregnancy were at increased risk of developing type 2 diabetes (Pettitt *et al.* 1993, Dabelea *et al.* 2000a, Lindsay *et al.* 2000). A further study involving 15 000 families showed a modest excess in maternal over paternal transmission of type 2 diabetes in a multiethnic population in the US, although the relationships varied between racial groups and appeared stronger in the female offspring (Karter *et al.* 1999). Excess maternal transmission of type 2 diabetes has been confirmed in some (Alcolado & Alcolado 1991, Lin *et al.* 1994, Thomas *et al.* 1994, Groop *et al.* 1996, Klein *et al.* 1996, Riley *et al.* 1997,

Bjornholt *et al.* 2000), but not all other populations (Mitchell *et al.* 1995, McCarthy *et al.* 1996, Viswanathan *et al.* 1996, Meigs *et al.* 2000). However, the association between maternal diabetes, offspring birth weight and subsequent diabetes is complex because gestational diabetes predisposes to macrosomic infants with higher birth weight (Silverman *et al.* 1991). Women of low birth weight are at increased risk of developing gestational diabetes and type 2 diabetes (Williams *et al.* 1999, Egeland *et al.* 2000, Forsen *et al.* 2000, Innes *et al.* 2002, Seghieri *et al.* 2002) and hence deliver larger babies (Seghieri *et al.* 2002). 'Macrosomic' offspring are themselves at risk of developing obesity (Pettitt *et al.* 1993, Gillman *et al.* 2003), gestational diabetes (Innes *et al.* 2002) and type 2 diabetes later in life (Pettitt *et al.* 1993, Lindsay *et al.* 2000, Catalano *et al.* 2003). Thus, some studies have confirmed a U-shaped relationship between a woman's risk for developing gestational diabetes and her own birth weight (Egeland *et al.* 2000, Innes *et al.* 2002). This may obscure inferences about intergenerational relationships between birth weight and risk of type 2 diabetes. The complexity of dissecting programmed from genetic phenomena is also most clearly illustrated in studies of diabetes risk, for example in the Pima Indian community in which there is a very high prevalence of maternal diabetes. In this population, low birth weight is associated with the subsequent development of type 2 diabetes, but only if paternal diabetes is also present (Lindsay *et al.* 2000). Maternal diabetes alone is still associated with an increased risk of type 2 diabetes in the offspring, but in individuals with higher rather than lower birth weight (Pettitt *et al.* 1993, Dabelea *et al.* 2000a, Lindsay *et al.* 2000). This suggests that it is paternal diabetes which is associated with lower offspring birth weight, and this has been confirmed in some (Yajnik *et al.* 2001, Hypponen *et al.* 2003), but not all (Rich-Edwards *et al.* 1999), further studies elsewhere. It has been inferred that the association of low birth weight and diabetes reflects the influence of genetic factors (Dunger *et al.* 1998, Hattersley & Tooke 1999). Indeed, it has recently been shown that in the Pima population, birth weight is linked to a locus on chromosome 11, with evidence for an imprinted, paternally expressed gene (Lindsay *et al.* 2002a). There is, however, little evidence of parent-specific linkage of diabetes at this locus, and indeed a number of genes associated with insulin resistance are not associated with birth weight in the Pima population (Lindsay *et al.* 2002b). Moreover, extrapolating findings in a population with very high genetic predisposition to diabetes to other populations may not be valid, since the relative importance of non-genetic mechanisms may be greater elsewhere.

Thus, although there are maternal and paternal effects on offspring birth weight and susceptibility to type 2 diabetes and cardiovascular disease which may be genetic and/or environmental, there is evidence for a specific influence of maternal rather than paternal characteristics

which may represent a process of intergenerational programming.

Intergenerational effects in animal models of programming

Observational studies have been of fundamental value in generating the hypotheses of the early life origins of disease. However, to dissect and validate mechanisms has required extensive animal studies (Benediktsson *et al.* 1993, Seckl 1997, 1998, Hoet & Hanson 1999, Challis *et al.* 2001, Meaney 2001). Although most attention has been given to the 'first generation' of offspring exposed to a manipulation when *in utero*, there is a substantial body of evidence from animal studies that programmed phenomena can be perpetuated in later generations. Animal models of prenatal programming by nutrition or exercise, and postnatal programming by nutrition or handling have shown effects on birth weight (Stewart *et al.* 1975, Pinto & Shetty 1995), glucose tolerance (Martin *et al.* 2000, Patel *et al.* 2001) and the hypothalamic-pituitary axis (Francis *et al.* 1999) in subsequent generations.

Programming of birth weight

Intergenerational effects of dietary manipulations on birth weight have been demonstrated in black-and-white hooded rats (Stewart *et al.* 1975) (Fig. 3). Colonies of rats were maintained for 12 generations on a control diet or a diet marginally deficient in protein. Birth weight was reduced in the first generation of malnourished animals and this effect of poor maternal diet on birth weight appeared to be amplified in subsequent generations. Mid-way through this intergenerational experiment a more unpalatable diet was introduced by chance. Following this, further reduction in birth weight was seen in the malnourished colony and in addition, there was a slight reduction in birth weight in the control colony. After the re-introduction of more palatable chow, birth weight in control animals increased, but did not return to baseline for approximately three generations despite the resumption of normal nutrition. The study demonstrates that continued poor maternal nutrition produces amplified effects on birth weight through a number of generations. However, the accidental introduction of less-palatable food, which resulted in a period of self-imposed calorie restriction in the 'control' animals, also provides evidence that poor nutrition in one generation can produce effects on birth weight in subsequent generations. This effect was confirmed in further experiments when a number of animals from the malnourished colony weaned onto the control diet did not achieve an adult size equivalent to that of the control animals for three further generations (Stewart *et al.* 1980).

Intergenerational effects on birth weight in rats have also been shown following maternal exercise during

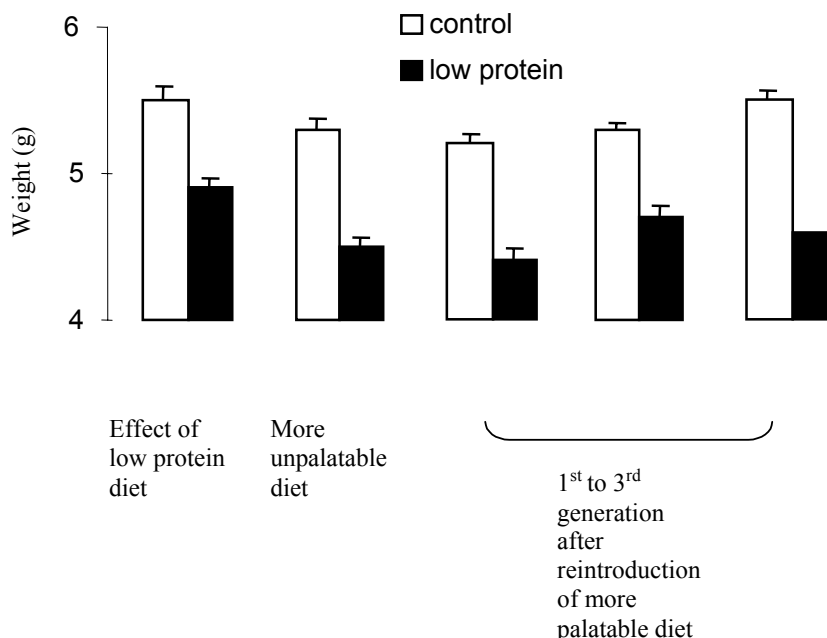


Figure 3 Intergenerational effects of protein deficiency on birth weight in rats. Rats from the same colony were maintained on a control diet or a diet marginally low in protein. F1 offspring of rats on the lower protein diet showed an immediate reduction in birth weight and thereafter showed a progressive reduction in birth weight over a number of generations. Additionally, for litters six and seven, a more unpalatable diet was accidentally introduced to both groups, leading to a reduction in birth weight in rats on the control diet, and a further reduction in birth weight in the malnourished group. Birth weights remained reduced in the control group for two further generations after a more palatable diet was re-introduced. (Adapted from Stewart *et al.* 1975.) Data are mean \pm S.E.M.

pregnancy and lactation (Pinto & Shetty 1995). Exercise during pregnancy (swimming) resulted in low birth weight first generation (F1) pups. The second generation (F2) offspring of growth-retarded F1 animals that were sedentary during pregnancy were also found to be growth retarded, suggesting an adverse intergenerational influence of maternal exercise stress on fetal growth in these animals.

Programming of metabolic parameters and blood pressure

Recent studies have demonstrated other intergenerational effects in animal models. Fetal undernutrition can produce effects on glucose homeostasis in an F2 generation of rats (Martin *et al.* 2000). Intergenerational effects on birth weight and the endocrine pancreas have also been reported following the use of a low protein, isocaloric diet (Hoet & Hanson 1999).

Intergenerational effects on blood pressure in rabbits have recently been demonstrated in an experiment in which females with surgically induced hypertension were mated with normotensive males (Denton *et al.* 2003). The female offspring of hypertensive rabbits had increased blood pressure as adults when compared with the offspring

of sham-operated females, although blood pressure in male offspring was unaffected (Denton *et al.* 2003).

Postnatal programming

Postnatal programming may also have intergenerational effects. Overfeeding in the neonatal period has been shown to produce second generation effects on glucose homeostasis (Laychock *et al.* 1995, Vadlamudi *et al.* 1995, Patel *et al.* 2001, Srinivasan *et al.* 2003).

Additionally, postnatal environmental manipulations programming the hypothalamic–pituitary–adrenal (HPA) axis stress response may produce intergenerational effects. A number of studies suggest that differences in behavioural and neuroendocrine responses to stress may be transmitted from one generation to another by non-genomic mechanisms (Meaney 2001). In rodents, naturally occurring variations in maternal behaviour are associated with different HPA stress responsiveness in offspring (Liu *et al.* 1997). Cross-fostering studies have demonstrated that such differences in maternal behaviour, and therefore differences in offspring stress reactivity, may be transmitted across generations by non-genomic mechanisms

(Francis *et al.* 1999). Additionally, postnatal handling of rat pups is associated with programming of the HPA axis; handled offspring show reduced HPA responses to stress and increased maternal care behaviour (Francis *et al.* 1999). Again, these individual differences in maternal behaviour and HPA responses can be transmitted from one generation to another (Francis *et al.* 1999).

Mechanisms of intergenerational inheritance

From the above, it is clear that intergenerational programming can occur, even in the absence of a continuing environmental stimulus. The evidence in animals is more clearcut than the evidence in humans, in part because of experimental design allowing controlled experiments and probably also because of the genetic homogeneity of animal colonies, in which confounding effects of genetic influences play a much smaller role. It appears that permanent 'programming' of maternal physiology may lead to the persistence of programming effects across a number of generations. Such effects might be advantageous, as in the secular changes of increasing birth weight across generations which have been documented in some populations (Chike-Obi *et al.* 1996, Skjaerven *et al.* 2000, Kramer *et al.* 2002), or deleterious, as in the perpetuation of low birth weight and higher blood pressure (Barker *et al.* 1989, Walker *et al.* 1998). Why might the environmental experience of one generation affect the offspring of subsequent generations, and how might such intergenerational effects be mediated? A model is presented in Fig. 1.

Maternal growth

Exposure of the fetus to an adverse environment *in utero* may lead to permanent alterations in physiology in adulthood. Such physiological changes may result in an adverse intrauterine environment for the offspring of the individual, leading to physiological changes in the next generation and so on. There is evidence that poor maternal intrauterine growth is associated with reduced weight gain during pregnancy (Hackman *et al.* 1983), suggesting that pregnancy may be affected by physiological changes consequent on poor maternal growth. The importance of maternal size in determining the intrauterine growth of offspring has been demonstrated with cross-breeding experiments in Shetland ponies and Shire horses (Walton & Hammond 1938). The offspring were smaller when the Shetland pony rather than the Shire horse was the mother, suggesting that maternal size has an important influence on the size of the offspring. Indeed, short women have small babies (Cawley *et al.* 1954), and British mothers whose stature equalled or exceeded that predicted from midparental height had bigger babies than mothers of smaller stature (Emanuel 1997). Animal studies have shown that

organ size is affected by intrauterine malnutrition (Stewart *et al.* 1975), and girls born small for gestational age and remaining small have reduced uterine and ovarian size (Ibanez *et al.* 2000). Reduced uterine size in growth-retarded females who do not demonstrate catch-up growth and who fail to attain the final height predicted from their genetic potential may therefore have intergenerational effects on birth weight.

However, the growth-retarded babies most likely to develop adult cardiovascular risk factors are those who catch up most in terms of growth in childhood. These mothers will not, therefore, be small at the time of conceiving the next generation, suggesting that maternal size is unlikely to account for intergenerational programming of cardiovascular risk.

Socio-economic factors

Socio-economic factors may have a role in intergenerational effects. Lifelong minority status and disadvantage amongst black women in the US may have played a key part in perpetuating poor intrauterine growth across a number of generations (Collins *et al.* 2002). In two Swedish cohorts born in the 1920s and in 1985, household social class was shown to have a clear influence on birth weight (Vagero & Leon 1994). However, social class is (at least conventionally) as much influenced by paternal as by maternal circumstances, so is unlikely to account for matrilineal inheritance.

Conversely, improvements in the environment and in maternal health could also have intergenerational effects on offspring growth. Secular trends in some populations show increases in mean birth weight of 40–100 g over decades (Chike-Obi *et al.* 1996, Skjaerven *et al.* 2000, Collins *et al.* 2002). Such a rapid increase in the mean population birth weight provides evidence of the importance of environmental factors in the expression of genetic potential.

Nutrition

One of the major factors proposed to explain fetal programming is maternal undernutrition, and studies in humans and animals suggest that this may have intergenerational consequences. There is no doubt that in developing countries, maternal diet can affect birth weight, and may be extremely important in mediating intergenerational effects on birth weight and adult disease. Such effects may also be mediated, or indeed amplified, by adverse environmental conditions persisting across a number of generations. In animal models, second generation effects have been noted following impaired nutrition *in utero*, and exposure during specific time-windows of development may be important (Stewart *et al.* 1975, 1980, Laychock *et al.* 1995, Hoet & Hanson 1999, Martin *et al.* 2000). However, these occur even when nutrition is

normal in the F2 generation, so that perpetuation of the insult may not be required to express the effect in later generations.

Initial results from the Dutch famine studies suggested that there may be second generation effects following a specific environmental insult in a previously healthy population (Lumey 1992). The effects of malnutrition have been reported widely following the Dutch famine of 1944–1945 when the Western Netherlands was affected by acute famine, a period known as the ‘Hunger Winter’. The famine ceased immediately with liberation in May 1945, after which food supplies became abundant. Initial studies suggested that mothers with first and second trimester exposure to famine later delivered offspring (F2) of lower birth weight than those not exposed to famine (Lumey 1992). However, this study was potentially flawed in a number of ways, including that birth weights in famine-exposed mothers were not directly ascertained but were extrapolated from another group. A subsequent study found no significant effect of maternal famine exposure on their F2 offspring birth weight (Stein & Lumey 2000).

In developed countries, dietary deficiency is rarely thought to be a significant cause of impaired fetal growth (Godfrey & Robinson 1998, Mathews *et al.* 1999, Robinson *et al.* 2000). However, recent studies suggest that women with eating disorders are more likely to give birth to low birth weight infants (Conti *et al.* 1998). Although dietary supplementation has been shown to increase birth weight in a study of women in the Gambia (Ceesay *et al.* 1997), most studies have only demonstrated a small effect (Kramer 2002). One small study in Guatemala has demonstrated that nutritional supplementation of girls during early childhood may have a positive effect on the birth weight and height of their offspring (Stein *et al.* 2003). Birth weight is influenced by maternal body composition as well as nutrition during pregnancy (Barker 1998) and it is likely that fetal development may be influenced by micronutrient as well as macronutrient deficiency (Boucher 1998). However, so far, single micronutrient supplementation trials have generally not shown a significant effect on birth weight (Fall *et al.* 2003, Merialdi *et al.* 2003).

Thus, the role of impaired nutrition in intergenerational effects on birth weight and cardiovascular risk remains uncertain, but may be particularly important in maintaining the cycle of intergenerational programming in developing countries.

Glucocorticoids

Another major hypothesis advanced to explain fetal programming effects is that of fetal glucocorticoid overexposure (Benediktsson *et al.* 1993, Edwards *et al.* 1996). Glucocorticoids are associated with long-term organisational effects, and glucocorticoid treatment during pregnancy has been shown to reduce birth weight in animals

(Reinisch *et al.* 1978, Ikegami *et al.* 1997, Nyirenda *et al.* 1998, Newnham *et al.* 1999, Newnham 2001). In rats, antenatal dexamethasone treatment leads to hypertension (Benediktsson *et al.* 1993), elevated hepatic gluconeogenic enzymes and impaired glucose tolerance in the adult offspring (Nyirenda *et al.* 1998, Cleasby *et al.* 2003). In fetal sheep its use has been associated with reduced birth weight, changes in blood pressure, altered insulin responses to a glucose challenge and delayed brain myelination (Dunlop *et al.* 1997, Newnham 2001).

Glucocorticoids are widely used in the management of women at risk of preterm delivery to enhance fetal lung maturation, and in the antenatal management of fetuses at risk of congenital adrenal hyperplasia. Human studies have confirmed that antenatal glucocorticoid administration is associated with a reduction in birth weight (French *et al.* 1999, Bloom *et al.* 2001), although normal birth weight has been reported in infants at risk of congenital adrenal hyperplasia who received low-dose dexamethasone *in utero* from the first trimester (Forest *et al.* 1993, Mercado *et al.* 1995). Antenatal glucocorticoid administration has also been linked with higher blood pressure in adolescence (Doyle *et al.* 2000).

Fetal undernutrition and fetal glucocorticoid overexposure may be linked by a common mechanism (Phillips *et al.* 1994, Langley-Evans *et al.* 1996). The enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β HSD 2) converts active glucocorticoids to inactive products, and is present in the placenta; the enzyme may act as a barrier to protect the fetus from maternal glucocorticoids (Benediktsson *et al.* 1993). Reduced placental 11 β HSD 2 gene expression has been reported in human pregnancies complicated by intrauterine growth retardation (Benediktsson *et al.* 1995, McTernan *et al.* 2001), and rodent studies have demonstrated that dietary restriction during pregnancy reduces placental 11 β HSD 2 expression (Langley-Evans *et al.* 1996) and disturbs the neonatal HPA axis (Lesage *et al.* 2001). Thus, maternal malnutrition potentially exerts programming effects by inducing fetal overexposure to the effects of maternal glucocorticoids.

Furthermore, in animal models (Nyirenda *et al.* 1998, Welberg *et al.* 2000) and in humans (Phillips *et al.* 1998, Levitt *et al.* 2000, Reynolds *et al.* 2001), plasma glucocorticoids are elevated in adults born with lower birth weight. As prenatal glucocorticoid exposure lowers birth weight and is associated with later hypertension in humans and animal models (Nyirenda *et al.* 1998, Doyle *et al.* 2000, Newnham 2001), elevated glucocorticoid levels might potentially mediate both lower birth weight and hypertension through a number of generations.

Blood pressure

Other possible mechanisms underlying intergenerational effects include haemodynamic changes, which may be self-perpetuating in subsequent generations. One such

mediator of this effect may be blood pressure; lower maternal birth weight is associated with an increased risk of hypertension during pregnancy (Klebanoff *et al.* 1999) and higher maternal blood pressure during pregnancy is associated with lower offspring birth weight (Churchill *et al.* 1997, Ferrer *et al.* 2000, Brown *et al.* 2001, Buchbinder *et al.* 2002), and with higher offspring blood pressure (Walker *et al.* 1998). In addition, maternal birth weight is related to offspring blood pressure (Barker *et al.* 2000). Although one study found that the association between maternal birth weight and offspring blood pressure was independent of maternal blood pressure later in life (Barker *et al.* 2000), this apparently inherited effect may represent intergenerational influences on fetal programming, with low birth weight and subsequent higher blood pressure influencing fetal growth in such a way as to perpetuate this phenomenon. Indeed this is supported by a recent study demonstrating higher blood pressure in the female offspring of rabbits with secondary hypertension (Denton *et al.* 2003).

Sex-specific effects

A number of sex-specific effects have been described in animal models of fetal programming (Hales *et al.* 1996, Dean & Matthews 1999, Kind *et al.* 1999, Lingas *et al.* 1999, Smith & Waddell 2000, Dean *et al.* 2001, Lingas & Matthews 2001, Liu *et al.* 2001, Owen & Matthews 2003), with females appearing to be more sensitive to some programming effects (Smith & Waddell 2000, Denton *et al.* 2003). Human studies have revealed some sex differences in the long-term disease risk associated with low birth weight (Forsen *et al.* 2000, Walker *et al.* 2002), or exposure to famine prenatally (Ravelli *et al.* 1999). Such sex-specific effects may represent the differential sensitivity of males and females to programming phenomenon and stronger programming in females may further amplify the matrilineal pattern of intergenerational inheritance.

Epigenetic mechanisms

Molecular mediators of programming of physiology by events in early life remain obscure, and any role in intergenerational programming is therefore speculative. Modification of the genome over and above alterations in nucleotide sequence, or 'epigenetic' modification, is thought to be important in maintaining different patterns of gene expression in different cell groups, in the establishment of the choice of parental allele expressed in germ cells and beyond (parental imprinting), and in the erasure of epimutations (Rakyan *et al.* 2001). Epigenetic control of gene expression is likely to be mediated by alterations in DNA methylation and/or modifications of chromatin packaging, possibly via changes in histone acetylation. Both mechanisms may influence transcriptional activity and thus gene expression, mainly by the transcriptional

silencing of the modified allele (Rakyan *et al.* 2001). Such modifications influence gene expression, are established early in development and maintained throughout life and may affect the phenotype without changing the DNA sequence, making them prime candidates to explain programming. Epigenetic modification is not restricted to parentally imprinted genes, and the variable expression of some identical alleles within a population may therefore be due to epigenetic modulation rather than genetic differences or adult environmental influences (Rakyan *et al.* 2001).

A number of genes important in modulating fetal growth, particularly those involved in the control of the expression of insulin-like growth factor (IGF)-II, are imprinted; indeed, loss of imprinting of the IGF-II gene in humans leads to Beckwith–Wiedemann syndrome, associated with fetal overgrowth. In addition, IGF-II and a number of related genes are imprinted in the placenta (Young 2001) and it has been proposed that the IGF-II gene and perhaps others may control the placental supply of nutrients to the fetus, and thus affect fetal growth (Constancia *et al.* 2002, Reik *et al.* 2003). In mice, manipulations leading to alterations in the expression of imprinted genes in fetal tissues and in the placenta have been shown to be associated with alterations in fetal growth (Reik *et al.* 2003). Imprinting of genes has been proposed as the mechanism behind the association of lower offspring birth weight with paternal diabetes in the Pima Indian population (Lindsay *et al.* 2000, 2002a), and in the parental differences seen in the transmission of class III alleles of the variable number tandem repeat minisatellite 5' to the insulin gene, variations in which have been associated with type 2 diabetes (Huxtable *et al.* 2000).

The epigenetic silencing of one allele of a gene according to the parent of origin, or parental imprinting, is usually thought to be erased through meiosis and re-established in the offspring. However, recent evidence suggests that epigenetic modifications at some other alleles may not be completely erased during gametogenesis and embryogenesis, potentially resulting in the intergenerational inheritance of the epigenetic state (Roemer *et al.* 1997, Morgan *et al.* 1999). Very recently it has been shown in mice that the variable expressivity of an allele affecting tail development corresponds with differential methylation, which shows transgenerational epigenetic inheritance after both paternal and maternal transmission, displays parent of origin effects (the penetrance of the abnormal tail phenotype is greater after paternal transmission) and is influenced by the strain background (Rakyan *et al.* 2003).

Imprinting of genes can be modified by environmental factors (Reik *et al.* 2003) and imprinted genes may be more vulnerable to methylation changes than the rest of the genome (Young 2001). Embryo culture experiments have shown that environmental influences can permanently affect gene expression and have profound effects on

growth (Reik *et al.* 1993, Dean *et al.* 1998, Khosla *et al.* 2001, Young *et al.* 2001). Manipulations of the culture medium of the pre-implantation embryo can result in fetal overgrowth in sheep, in association with reduced methylation and a consequent reduction in expression of the IGF-II receptor gene (Young *et al.* 2001), and reduction in fetal weight associated with reduced expression of IGF-II and H19 in mice (Khosla *et al.* 2001), perhaps representing epigenetic mechanisms affecting fetal growth. Intriguingly, many growth factors, including IGF-II, are regulated by glucocorticoids in fetal and adult tissues *in vivo* and *in vitro* (Luo *et al.* 1990, Li *et al.* 1993, 2002, Miell *et al.* 1994, Mouhieddine *et al.* 1996, Forhead *et al.* 1998). Offspring IGFs are also affected by maternal nutrition in rats (Woodall *et al.* 1996, Petrik *et al.* 1999) and in humans (Barker *et al.* 1993). Very recently, altered maternal diet during pregnancy has been shown to increase methylation of the agouti gene and alter the phenotype of Agouti Yellow mouse pups. These mice are obese and yellow, due to a mutation in the agouti gene; however, pups born to mothers supplemented with vitamins during pregnancy were found to be thin and brown, and had altered methylation at the agouti locus (Waterland & Jirtle 2003).

Thus, environmental factors including nutrition and glucocorticoid exposure in the fetus could potentially influence the expression of genes, affecting fetal growth and later disease risk. If such epigenetic modifications were not erased during gametogenesis and embryogenesis, this could lead to the transgenerational inheritance of 'programmed effects' (Reik *et al.* 2003). Indeed, nutrition-mediated epigenetic effects have been proposed as a mechanism to explain the apparent transgenerational inheritance through the male line of cardiovascular disease and diabetes risk described in Swedish men (Kaati *et al.* 2002, Pembrey 2002). Furthermore, evidence is emerging for selective methylation/demethylation of specific promoters of the glucocorticoid receptor gene in association with variations in maternal care (Weaver *et al.* 2002) which also appear to be inherited.

Intergenerational programming and disease in transitional populations

The thrifty phenotype hypothesis includes the concept that 'the poorly nourished mother essentially gives the fetus a forecast of the nutritional environment into which it will be born' (Hales & Barker 2001). Intergenerational phenomena would favour infant survival, providing for transfer of information on the extra-uterine environment from mother to fetus. Physiological adaptations prepare the fetus for the same extra-uterine conditions, optimising survival at least until after reproduction, under conditions of stress or deprivation. Such non-genomic influences on fetal growth and development acting across a number of generations would help to ensure continued population

survival, and whilst manifest in both sexes, would be most important in the female line, to optimise reproductive capacity.

However, these intergenerational effects of fetal programming would only be advantageous to population survival when environmental conditions remain consistent over several generations. Any rapid change in the environment puts the 'programmed' offspring at risk of hypertension and glucose intolerance, and the risk of these conditions is amplified by obesity. This is clearly seen in developing countries where peoples leading 'traditional' lifestyles have a low prevalence of type 2 diabetes (King & Rewers 1993). The prevalence of diabetes, hypertension and cardiovascular disease in such populations increases rapidly with urbanisation or migration to other countries, associated with changes in diet, exercise and the resultant increase in obesity (Cruickshank *et al.* 2001, Fall 2001). In addition, migrant populations are more likely to live in poor social conditions, with reduced access to health care (Greenhalgh 1997).

Thus, among populations in developing countries who continue to live traditional lifestyles, 'programming' of the fetus would continue to be advantageous under conditions of environmental deprivation, and a cycle of intergenerational programming may result (Fig. 1). Rapid urbanisation of such populations, however, would lead to an increase in the prevalence of type 2 diabetes and other cardiovascular risk factors. Indeed, such effects have been noted in many ethnic groups, and have been particularly studied in the Pima Indian population of Arizona and the Polynesian and Micronesian populations, who have a very high prevalence of obesity and type 2 diabetes. In addition, gestational diabetes is more common among those who have moved from non-industrialised to industrialised societies (Fall 2001). In females, this increased risk of type 2 diabetes or gestational diabetes is likely to result in macrosomic offspring, themselves at increased risk of glucose intolerance in later life.

The thrifty phenotype hypothesis also predicts that improved environmental conditions would eventually lead to a decline in the prevalence of conditions such as type 2 diabetes and other cardiovascular risk factors, as better maternal health and nutrition result in improved fetal growth. Maternal physiology may respond to improvements in the environment in a manner that regulates fetal development, leading to improved fetal growth, and lowering the risk of the metabolic complications associated with low birth weight. Indeed this appears to be so in a number of developed countries, in which the transition from 'traditional lifestyles' to modern society has been very slow. The secular changes of increasing birth weight noted over a number of generations in some populations (Chike-Obi *et al.* 1996, Skjaerven *et al.* 2000, Kramer *et al.* 2002) may be due to improved nutrition and affluence. Additionally, in a number of developed countries, there has been a steady decline in the incidence of cardiovascular

disease (Tunstall-Pedoe *et al.* 1999) which has occurred too fast to be a result of genetic change. There is no doubt an important influence of changes in environmental factors affecting adult disease, but there may also be a contribution related to improved fetal and postnatal nutrition. In contrast, the prevalence of type 2 diabetes is increasing in developed countries; however, this is likely to be secondary to the epidemic of obesity in the developed world (Fall 2001).

Evidence from the Nauruan population provides further support for the suggestion that the intergenerational effects of fetal programming on glucose tolerance might be self-limiting. The Nauruans are a small Pacific Island population who suffered nutritional deficiency and drought before and during World War II. With the advent of affluence in the post-war years nutrition improved, and from the 1950s the population suffered an epidemic of obesity and glucose intolerance. Evidence from a survey of the islanders in 1987 suggested that the extremely high incidence of glucose intolerance and type 2 diabetes may be declining (Dowse *et al.* 1991). Although there has been no change in the prevalence of obesity, and no increase in exercise, there has been a marked decrease in the prevalence of impaired glucose tolerance. The authors speculate that this may be due to a genetic effect, suggesting that the females with impaired glucose tolerance are less fertile and have a smaller number of live births than women with normal glucose tolerance. This change has occurred very rapidly and an alternative explanation could be that improved fetal and infant nutrition consequent on affluence leads to fewer individuals who are at risk of diabetes because of intrauterine programming (Ozanne & Hales 1998). In contrast, the lack of such an effect in the Pima Indian population (Dabelea *et al.* 2000b) may be due to differences in the underlying genetic predisposition to diabetes in these different populations.

Thus, there are a number of potential outcomes of fetal programming. Low birth weight babies who do not exhibit catch-up growth are themselves more likely to give birth to low birth weight babies, demonstrating an intergenerational effect on birth weight. In contrast, low birth weight babies who do exhibit catch-up growth, particularly those who become obese, are at increased risk of cardiovascular disease. Women who develop type 2 diabetes or gestational diabetes are likely to give birth to macrosomic infants, themselves at risk of type 2 diabetes later in life. Such consequences may be seen with the rapid urbanisation of populations as described. Finally, populations exposed to a gradual improvement in the environment over a number of generations are more likely to avoid these consequences.

Conclusions

The association between low birth weight and subsequent disease has been well documented; however, it is also clear

that fetal programming effects may not be limited to the first generation. Indeed, intergenerational effects may masquerade as a genetic predisposition to cardiovascular disease in subsequent generations. There is some evidence from human studies that non-genetic effects may be associated with the intergenerational transmission of disease risk. However, any impact of such intergenerational effects will result from the interaction of genes and the pre- and postnatal environment, and will also occur against a heterogeneous background of genetic susceptibility. Thus, the importance of any effects in different populations will be variable, and it will be difficult to tease out the relative importance of each in any one human population. Nevertheless, there is compelling evidence from animal studies that non-genomic intergenerational effects could operate to produce programming effects across a number of generations.

Intergenerational effects of fetal programming may have major public health implications for developed and developing worlds. Additionally, there may be unforeseen long-term and intergenerational effects of interventions that impact on early human development. Finally, policies aimed at improving the health of one generation, in particular those directed at improving maternal, fetal and infant health and at reducing obesity, may have important benefits for a number of succeeding generations.

Acknowledgements

A J D and B R W are British Heart Foundation Research Fellows.

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Received in final form 12 September 2003

Accepted 18 September 2003

Made available online as an

Accepted Preprint 26 September 2003