

In utero programming of chronic disease

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A B S T R A C T

1. Many human fetuses have to adapt to a limited supply of nutrients. In doing so they permanently change their structure and metabolism.
2. These 'programmed' changes may be the origins of a number of diseases in later life, including coronary heart disease and the related disorders stroke, diabetes and hypertension.
3. This review examines the evidence linking these diseases to fetal undernutrition and provides an overview of previous studies in this area.

PROGRAMMING THE FETUS

In fetal life the tissues and organs of the body go through what are called 'critical' periods of development [1]. Critical periods may coincide with periods of rapid cell division. 'Programming' describes the process whereby a stimulus or insult at a critical period of development has lasting or lifelong effects [2,3]. The development of the sweat glands provides an interesting example of this process [4]. In the early years of this century Japanese military expansion took their soldiers and settlers into unfamiliar climates. They found that there were wide differences in people's abilities to adapt to hot climates. Physiological studies showed that this was related to the number of functioning sweat glands. People with more functioning sweat glands cooled down faster. Rather than attributing the differences in sweat gland numbers to 'genetic effects', Japanese physiologists explored the early development of the glands. They found that at birth all humans have similar numbers of sweat glands; but none of them function. In the first 3 years after birth a proportion of the glands become functional depending on the temperatures to which the child is exposed. The hotter the conditions the greater the number of sweat glands that are programmed to function. After 3 years the

programming is complete and the number of sweat glands is fixed. The development of sweat glands encapsulates the essence of programming – a critical period when the system is plastic and sensitive to the environment, followed by loss of plasticity and a fixed functional capacity.

THE UNDERNOURISHED FETUS

It is unquestionable that undernutrition is one of the influences which programme the human body and has lifelong consequences. Rickets has for a long while served as a demonstration that undernutrition at a critical stage of early life leads to persisting changes in structure. What is new is the recent realization that some of the body's 'memories' of early undernutrition become translated into pathology and thereby determine disease in later life [5]. This is perhaps unsurprising given the numerous animal experiments showing that undernutrition *in utero* leads to persisting changes in blood pressure, cholesterol metabolism, insulin response to glucose, and a range of other metabolic, endocrine and immune functions known to be important in human disease [2,6].

Key words: coronary heart disease, diabetes, fetus, hypertension, programming, undernutrition.

Abbreviation: IGF, insulin-like growth factor.

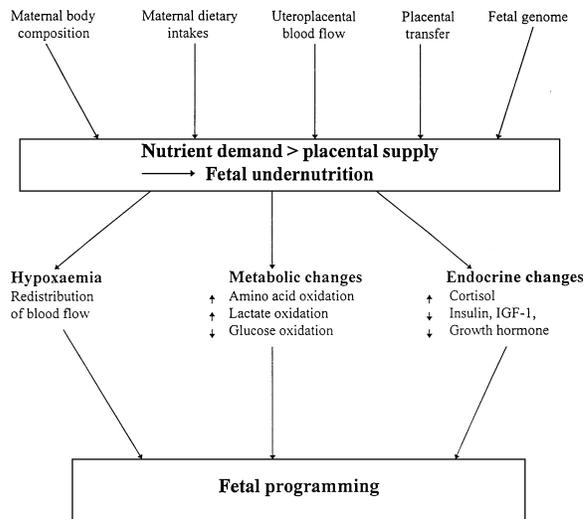


Figure 1 Fetal adaptations to undernutrition: a framework

Metabolic changes

The human fetus adapts to undernutrition by metabolic changes, redistribution of blood flow and changes in the production of fetal and placental hormones which control growth [7]. These adaptations are shown in Figure 1. The immediate metabolic response of the fetus to undernutrition is catabolism: it consumes its own substrates to provide energy [8]. More prolonged undernutrition leads to a slowing in growth. This enhances the fetus's ability to survive by reducing the use of substrates and lowering the metabolic rate. Slowing of growth in late gestation leads to disproportion in organ size since organs and tissues that are growing rapidly at the time are affected the most. Undernutrition in late gestation may, for example, lead to reduced growth of the kidney which is developing rapidly at that time. Reduced replication of kidney cells may permanently reduce cell numbers, because after birth there seems to be no capacity for renal cell division to 'catch up' [9,10].

Animal studies show that a variety of different patterns of fetal growth result in similar birth size. For example, a fetus that grows slowly throughout gestation may have the same size at birth as a fetus whose growth was arrested for a period and then 'caught up'. Different patterns of fetal growth will have different effects on the relative size of different organs at birth, even though overall body size may be the same. This emphasizes the severe limitation of birthweight as a measure of fetal growth.

Redistribution of blood flow

While slowing its rate of growth the fetus may protect tissues that are important for immediate survival, especially the brain. One way in which the brain can be protected is by redistribution of blood flow in its favour

[11,12]. This adaptation is known to occur in many mammals but in humans it has exaggerated costs for tissues other than the brain, notably the liver and other abdominal viscera, because of the large size of the human brain.

Endocrine changes

It is becoming increasingly clear that nutrition has profound effects on fetal hormones, and on the hormonal and metabolic interactions between the fetus, placenta and mother on whose co-ordination fetal growth depends [8]. Fetal insulin and the insulin-like growth factors (IGFs) are thought to have a central role in the regulation of growth and respond rapidly to changes in fetal nutrition [13]. If a mother decreases her food intake, fetal insulin, IGF and glucose concentrations fall, possibly through the effect of decreased maternal IGF. This leads to reduced transfer of amino acids and glucose from mother to fetus, and ultimately to reduced rates of fetal growth [14]. In late gestation and after birth the fetus' growth hormone and IGF axis take over, from insulin, a central role in driving linear growth. Although undernutrition leads to a fall in the concentrations of hormones that control fetal growth, it also leads to a rise in cortisol, whose main effects are on cell differentiation [7].

CORONARY HEART DISEASE AND STROKE

An important clue suggesting that coronary heart disease might originate during fetal development came from studies of death rates among babies in Britain during the early 1900s [15]. The usual certified cause of death in newborn babies at that time was low birthweight. Death rates in the newborn differed considerably between one part of the country and another, being highest in some of the northern industrial towns and the poorer rural areas in the north and west. This geographical pattern in death rates was shown to closely resemble today's large variations in death rates from coronary heart disease, variations that form one aspect of the continuing north/south divide in health in Britain [15]. One possible conclusion suggested by this observation was that low rates of growth before birth are in some way linked to the development of coronary heart disease in adult life. The suggestion that events in childhood influence the pathogenesis of coronary heart disease was not new. A focus on intrauterine life, however, offered a new point of departure for research.

The early epidemiological studies that pointed to the possible importance of programming in coronary heart disease were based on the simple strategy of examining men and women in middle and late life whose body measurements at birth were recorded. The birth records

Table 1 Death rates from coronary heart disease among 15726 men and women according to birthweight

Dashes are used in column one to indicate that the beginning of the range of values can be inferred from the last value in the preceding category.

Birthweight, lb (kg)	Standardized mortality ratio	No. of deaths
≤ 5.5 (2.50)	100	57
–6.5 (2.95)	81	137
–7.5 (3.41)	80	298
–8.5 (3.86)	74	289
–9.5 (4.31)	55	103
> 9.5 (4.31)	65	57
All	74	941

on which these studies were based came to light as a result of the Medical Research Council's systematic search of the archives and records offices of Britain – a search that led to the discovery of three important groups of records in Hertfordshire, Preston and Sheffield. The Hertfordshire records were maintained by health visitors and include measurements of growth in infancy as well as birthweight. In Preston and Sheffield detailed obstetric records documented body proportions at birth [16,17].

Sixteen-thousand men and women born in Hertfordshire during 1911–1930 have now been traced from birth to the present day. Death rates from coronary heart disease fell 2-fold between those at the lower and upper ends of the birthweight distribution (Table 1) [18]. A study in Sheffield showed that it was people who were small at birth because they failed to grow, rather than because they were born early, who were at increased risk of the disease [17]. The association between low birthweight and coronary heart disease has been confirmed in studies of men in Uppsala, Sweden [19], and Caerphilly, Wales [20] and among women in the U.S.A. Among 80000 women in the American Nurses Study there was a similar 2-fold fall in the relative risk of non-fatal coronary heart disease across the range of birthweights [21]. An association between low birthweight and prevalent coronary heart disease has recently been shown in a study in South India [22]. Among Indian men and women aged 45 years and over the prevalence of the disease fell from 18% in those who weighed 5.5 lbs (2.5 kg) at birth to 4% in those who weighed 7 lbs (3.2 kg) or more.

BODY PROPORTIONS AT BIRTH AND CARDIOVASCULAR DISEASE

The Hertfordshire records and the Nurses and Caerphilly studies did not include measurements of body size at birth other than weight. The weight of a newborn baby without a measure of its length is as crude a summary of its physique as is the weight of a child or adult without a

Table 2 Standardized mortality ratios for coronary heart disease in 3302 Finnish men born during 1924–1933

Dashes are used in column one to indicate that the beginning of the range of values can be inferred from the last value in the preceding category.

Birthweight, kg (lb)	ratio (no. of deaths)
≤ 2.5 (5.5)	84 (11)
–3.0 (6.6)	83 (44)
–3.5 (7.7)	99 (124)
–4.0 (8.8)	76 (80)
> 4.0 (8.8)	66 (27)
All	85 (286)
<i>P</i> value for trend	0.09

Term babies only	Standardized mortality ratio (no. of deaths)
Ponderal index at birth (kg/m ³)	
≤ 25	116 (59)
–27	105 (88)
–29	72 (64)
> 29	56 (33)
All	86 (244)
<i>P</i> value for trend	< 0.0001

measure of height. The addition of birth length allows the thin or stunted baby to be distinguished from the short, fat baby. With the addition of head circumference the baby whose body is small in relation to its head, as a result of 'brain-sparing', can also be distinguished. Thinness, stunting and a small trunk reflect differing fetal adaptations to undernutrition, hypoxia and other influences and they have different long-term consequences.

In Sheffield death rates for coronary heart disease were higher in men who were stunted at birth [23]. The mortality ratio for coronary heart disease in men who were 18.5 inches (47 cm) or less in length was 138 compared with 98 in the remainder [23]. Thinness at birth, as measured by a low ponderal index (birthweight/length³), was also associated with coronary heart disease. Table 2 shows that among men born in Helsinki, Finland, although low birthweight was associated with increased death rates for coronary heart disease, there was a stronger association with thinness at birth, especially in men born at term [24]. Men who were thin at birth, measured by a low ponderal index (birthweight/length³), had death rates that were twice those of men who had a high ponderal index.

In Finland raised death rates from coronary heart disease were associated with low placental weight. In Sheffield, however, coronary heart disease did not vary with placental weight but showed a U-shaped relation with the ratio of placental weight to birthweight, the highest mortality ratios being at either end of the distribution. The pattern of body proportions at birth which predicts death from coronary heart disease may be

Table 3 Prevalence of Type II diabetes and impaired glucose tolerance in men aged 59–70 years

Dashes are used in column one to indicate that the beginning of the range of values can be inferred from the last value in the preceding category.

Birthweight, lb (kg)	No. of men	% with impaired glucose tolerance or diabetes	Odds ratio adjusted for body mass index (95% confidence interval)
≤ 5.5 (2.50)	20	40	6.6 (1.5 to 28)
–6.5 (2.95)	47	34	4.8 (1.3 to 17)
–7.5 (3.41)	104	31	4.6 (1.4 to 16)
–8.5 (3.86)	117	22	2.6 (0.8 to 8.9)
–9.5 (4.31)	54	13	1.4 (0.3 to 5.6)
> 9.5 (4.31)	28	14	1.0
All	370	25	

therefore summarized as a small head circumference, stunting or thinness, which reflect retarded fetal growth, and either low placental weight or an altered ratio of placental weight to birthweight. The pattern for stroke, which has only been reported in Sheffield, is different. Whereas stroke is similarly associated with low birthweight it was not associated with thinness or shortness. Instead there were increased rates among men who had a low ratio of birthweight to head circumference, or a low ratio of placental weight to head circumference [23]. One interpretation of these associations is that normal head growth has been sustained at the cost of interrupted growth of the body in late gestation, in association with inadequate growth of the placenta.

Confounding variables

These findings suggest that influences linked to early fetal and placental growth have an important effect on the risk of coronary heart disease and stroke. It has been argued, however, that people whose growth was impaired *in utero* and during infancy may continue to be exposed to an adverse environment in childhood and adult life, and it is this later environment that produces the effects attributed to programming [5–28]. There is strong evidence that this argument cannot be sustained. In three of the studies which have replicated the association between birthweight and coronary heart disease, data on lifestyle factors including smoking, employment, alcohol consumption and exercise were collected [19–21]. Allowance for them had little effect on the association between birthweight and coronary heart disease.

In studies exploring the mechanisms underlying these associations, the trends in coronary heart disease with birthweight were found to be paralleled by similar trends in two of its major risk factors – hypertension and Type II diabetes mellitus [29,30]. Table 3 illustrates the size of these trends, the prevalence of Type II diabetes mellitus and impaired glucose tolerance falling 3-fold between

men who weighed 5.5 lbs at birth and those who weighed 9.5 lbs [29]. These associations with small size at birth are again independent of social class, cigarette smoking and alcohol consumption. Influences in adult life, however, add to the effects of the intrauterine environment. For example, the prevalence of impaired glucose tolerance is highest in people who had low birthweight but become obese as adults.

HYPERTENSION

Associations between low birthweight and raised blood pressure in childhood and adult life have been extensively demonstrated around the world. Figure 2 shows the results of a systematic review of published papers describing the association between birthweight and blood pressure [31] – a review based on 34 studies of more than 66 000 people of all ages in many countries. Each point on the figure with its confidence interval represents a study population and the populations are ordered by their ages. The horizontal position of each population describes the change in blood pressure that was associated with a 1 kg (2.2 lb) increase in birthweight. In almost all the studies an increase in birthweight was associated with a fall in blood pressure; and there was no exception to this in the studies of adults which now total nearly 8000 men and women. The associations are less consistent in adolescence, presumably because the tracking of blood pressure from childhood through adult life is perturbed by the adolescent growth spurt. These associations were not confounded by socio-economic conditions at the time of birth or in adult life [32]. The difference in systolic blood pressure associated with a 1 kg difference in birthweight was around 3.5 mmHg. In clinical practice this would be a small difference but these are large differences between the mean values of populations. Available data suggest that lowering the mean systolic

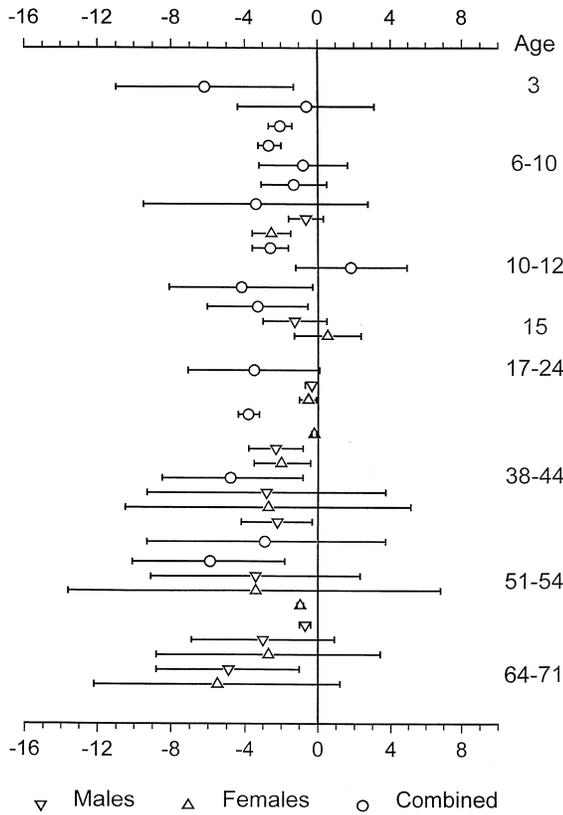


Figure 2 Difference in systolic blood pressure (mmHg), with confidence intervals, per kg increase in birthweight (adjusted for weight in children and body mass index in adults) in published studies of people of different ages

pressure in a population by 10 mmHg would correspond to a 30% reduction in total attributable mortality [33].

The association between low birthweight and raised blood pressure depends on babies who were small for dates, after reduced fetal growth, rather than on babies who were born pre-term [16,34]. Although in these studies alcohol consumption and higher body mass were also associated with raised blood pressure, the associations between birthweight and blood pressure were independent of them. Nevertheless body mass remains an important influence on blood pressure and, in humans

and animals, the highest pressures are found in people who were small at birth but become overweight as adults.

As has already been discussed birthweight is a crude measure of fetal growth that does not distinguish stunting and thinness, differences in head size, or variations in the balance of fetal and placental size. Analyses in Preston defined two groups of babies who develop raised blood pressures [35,36]. The first group are thin with a low ponderal index (birthweight/length³) and a below-average head circumference. The second have a short crown-heel length in relation to their head circumference, and therefore a high head circumference to length ratio. Short babies tend to be fat and may have above average birthweight. In contrast to the associations between birth size and coronary heart disease, those between birthweight and blood pressure are generally as strong as those between thinness, stunting and blood pressure. Associations between blood pressure and thinness and stunting have been found in some studies [37] but not in others [38]. In a longitudinal study of young people in Adelaide, associations between blood pressure and thinness and stunting were not apparent at 8 years of age but emerged at 20 years (V. M. Moore, personal communication).

Placental size and blood pressure

Table 4 shows the systolic blood pressure of a group of men and women who were born, at term, in Sharoe Green Hospital in Preston, 50 years ago [16,35]. The subjects are grouped according to their birthweights and placental weights. Consistent with findings in other studies, systolic blood pressure falls between subjects with low and high birthweights. In addition, however, there is an increase in blood pressure with increasing placental weight. Subjects with a mean systolic blood pressure of 150 mmHg or more, a level sometimes used to define hypertension in clinical practice, comprise a group who as babies were relatively small in relation to the size of their placentas. There are similar trends with diastolic pressure. A rise in blood pressure with increasing placental weight was also found in 4-year-old children in Salisbury, U.K., and among 8-year-old

Table 4 Mean systolic blood pressure (mmHg) of men and women aged 50 years, born after 38 completed weeks of gestation, according to placental weight and birthweight

A dash is used in column one to indicate that the beginning of the range of values can be inferred from the last value in the preceding category. *S.D. = 20.4. Numbers of subjects are given in parentheses in the body of the Table.

Birthweight, lb (kg)	Placental weight, lb (g)				All
	≤ 1.0 (454)	1.25 (568)	1.5 (681)	> 1.5 (681)	
≤ 6.5 (2.9)	149 (24)	152 (46)	151 (18)	167 (6)	152 (94)
-7.5 (3.4)	139 (16)	148 (63)	146 (35)	159 (23)	148 (137)
> 7.5 (3.4)	131 (3)	143 (23)	148 (30)	153 (40)	149 (96)
All	144 (43)	148 (132)	148 (83)	156 (69)	149* (327)

children in Adelaide, Australia [37,39]. In studies of children and adults the association between placental enlargement and raised blood pressure has, however, been inconsistent [40]. For example, in a study of men and women born in Aberdeen, Scotland, after the Second World War, at a time when food was still rationed, raised blood pressure was associated with small placental size [41]. Animal studies offer a possible explanation of this inconsistency. In sheep the placenta enlarges in response to moderate undernutrition in mid-pregnancy [42,43]. This is thought to be an adaptive response to extract more nutrients from the mother. It is not, however, a consistent response but occurs only in ewes that were well nourished before pregnancy.

Mother's blood pressure

In some studies the blood pressures of the mothers during and after pregnancy have been recorded [37,44,45]. They correlate with the offspring's blood pressure. However, the associations between body size and proportions at birth and later blood pressure are independent of the mothers' blood pressures. Recent observations show that if the mother's blood pressure is measured throughout a 24-h period, rather than by isolated readings at antenatal clinics, there is a continuous inverse association between birthweight and maternal blood pressure [46]. It could be argued, therefore, that the association between low birthweight and raised blood pressure reflects an association, possibly genetic, between a mother's ambulatory blood pressure and the blood pressure of her offspring. The demonstration that experimental undernutrition during gestation programmes blood pressure in animals [47] argues against this interpretation; and an alternative explanation is that raised blood pressure during pregnancy reflects failure of maternal cardiovascular adaptations to pregnancy, which include peripheral vasodilatation, with consequent fetal undernutrition, low birthweight and raised blood pressure in the offspring.

Fetal undernutrition and blood pressure

Several lines of evidence support the thesis that it is poor delivery of nutrients which programmes raised blood pressure in humans. Maternal height, parity and cigarette smoking, which influence fetal growth, have not been found to be related to the offspring's blood pressure other than in small pre-term babies [37,48]. In Jamaica, children whose mothers had thin triceps skinfolds in early pregnancy and low weight gain during pregnancy had raised blood pressure [49]. There were similar findings in a group of children in Birmingham [50]. In the Gambia low weight gain in pregnancy was associated with higher blood pressure in childhood [51]. In Aberdeen, Scotland, the blood pressures of middle-aged

men and women were found to be related to their mother's intakes of carbohydrate and protein during pregnancy [41].

Childhood growth

There are a number of possible mechanisms by which restricted intrauterine growth could either initiate or amplify raised blood pressure. Studies in the U.S.A., the U.K. and Holland have shown that blood pressure in childhood predicts the likelihood of developing hypertension in adult life. These predictions are strongest after adolescence. In children the rise of blood pressure with age is closely related to growth and is accelerated by the adolescent growth spurt. These observations have led Lever and Harrap [52] to propose that essential hypertension is a disorder of growth. The hypothesis that hypertension is a disorder of accelerated childhood growth can be reconciled with the association with low birthweight by postulating that postnatal catch-up growth plays an important role in amplifying changes established *in utero*.

Renin-angiotensin system

There is evidence that the fetal renin-angiotensin system is activated during intrauterine growth retardation [53]. However, in a follow-up study of men and women born in Sheffield, those who had been small at birth had lower plasma concentrations of inactive and active renin [54]. Causes of raised blood pressure that are not mediated by increased rates of renin release tend to result in low concentrations of renin, and therefore, at first sight, these findings suggest that the association between impaired fetal growth and raised blood pressure must involve mechanisms other than the renin-angiotensin system. However, low concentrations of renin in adult life do not exclude the possibility that the renin-angiotensin system has exerted an earlier but lasting influence.

Renal structure

An alternative explanation for the low plasma renin concentrations in people who were small at birth is that they reflect a relative deficit of nephrons. Brenner and co-workers [55,56] have suggested that retarded fetal growth leads to reduced numbers of nephrons which in turn leads to increased pressure in the glomerular capillaries and the development of glomerular sclerosis. This sclerosis leads to further loss of nephrons and a self-perpetuating cycle of hypertension and progressive glomerular injury. The numbers of nephrons in the normal population varies widely, from 300 000 to 1 100 000 or more [55]. Animal and human studies have shown that low rates of intrauterine growth are associated with reduced numbers of nephrons [57]. Studies using fetal

ultrasound have shown that babies that are small for gestational age have reduced renal growth during the critical period of 26 to 34 weeks of gestation. This reduces the antero-posterior size of the kidney but does not diminish kidney length [58]. It has been suggested that during normal childhood development kidney growth lags behind the increases in body weight, and blood pressure rises in order to maintain renal homeostasis [59].

Endocrine

Animal studies have led to the hypothesis that fetal undernutrition leads to lifelong changes in the fetus' hypothalamic-pituitary-adrenal axis which in turn resets homeostatic mechanisms controlling blood pressure [60,61]. A recent study of 9-year-old children in Salisbury showed that those who had been small at birth had increased urinary adrenal androgen and glucocorticoid metabolite excretion [62], preliminary evidence that the hypothalamic-pituitary-adrenal axis is programmed in humans. The growth hormone insulin-like growth factor-1 (IGF-1) axis may also be programmed *in utero*. Children who had low birthweight have raised plasma IGF-1 concentrations [48,63]. The highest concentrations are in children who had the lowest birthweights but attain the largest body size in childhood. Raised IGF-1 concentrations may therefore be linked to catch-up growth. IGF-1 is known to be important for the growth of blood vessels [64], and raised concentrations could be one of the processes underlying the suggested association between catch-up growth and raised blood pressure in later life.

Vascular structure

The elastic recoil of the aorta is important in maintaining blood flow in the peripheral circulation and in the coronary arteries during diastole. Reduced elasticity (compliance) in the aorta is a marker of cardiovascular disease [65]. It is associated with hypertension, and also with left ventricular hypertrophy because the work of the left ventricle is increased [66,67]. Fifty-year-old men and women in Sheffield who were small at birth had reduced compliance in the large arteries of the trunk and legs [44]. Martyn and Greenwald [68] have proposed that impaired synthesis of the scleroprotein elastin is one of the mechanisms underlying the association between low birthweight and raised blood pressure. The elasticity of larger arteries largely depends on elastin [69], which is laid down *in utero* and during infancy and thereafter turns over slowly [69]. Its half-life in humans is approximately 40 years [70]. Reduced elastin deposition leads to less compliant, that is 'stiffer', arteries which will lead to raised blood pressure. The loss of elastin with ageing will amplify the increase in blood pressure.

In the growth-retarded fetus there are changes in blood flow in several vascular beds, including the descending aorta and cerebral vasculature [71]. These are a 'brain-sparing' adaptation which lead to preferential perfusion of the brain at the expense of the trunk [11,12,72]. If sustained they may lead to reduced growth of the abdominal viscera and stunting at birth. Because elastin deposition in a blood vessel *in utero* is related to the flow of blood, reduced flow in the large arteries of the trunk and legs as a consequence of 'brain-sparing' may be associated with reduced elastin deposition, less compliant arteries, and consequent hypertension. Diversion of oxygenated blood away from the trunk to sustain the growth of the brain increases peripheral resistance [71,73], and echocardiography has shown that growth-retarded fetuses have hypertrophy of both ventricles [74,75]. Cardiac myocytes become terminally differentiated before birth and their rate of maturation is influenced by the load on the heart. Early pressure loading leads to fewer, but larger, myocytes. Left ventricular enlargement is known to be a strong predictor of morbidity and death from coronary heart disease independently of its association with raised systolic blood pressure and increased body mass [76]. Among 67-year-old men in Hertfordshire, those who had had low weight at 1 year had concentric enlargement of the left ventricle [77]. This may reflect the long-term effects of prenatal blood diversion to the brain in a baby that is stunted at birth and whose growth does not catch up in infancy. An association between low weight around the age of 1 year and later concentric left ventricular hypertrophy has been confirmed in a sample of children and adults in Lorraine, France [78].

Recent studies suggest that low birthweight is associated with persisting alterations in vascular structure and function in addition to its associations with compliance. Among men in Hertfordshire those who had had low birthweight had narrow bifurcation angles in their retinal blood vessels [79]. People with hypertension have similar changes in retinal vascular geometry. In a study of children in the U.K., those who had low birthweight had reduced flow-mediated dilation in the brachial artery after the artery had been occluded and released. Flow-mediated dilation depends on the endothelium. These findings suggest, therefore, a link between low birthweight and endothelial dysfunction [80].

Nervous system

People with high blood pressure tend to have a high resting pulse rate [81]. This is associated with high cardiac output, hyperdynamic circulation and features of increased sympathetic nervous system activity [82]. Among men and women in Preston, those who had low birthweight had a higher resting pulse rate [83]. This is consistent with the hypothesis that increased sympathetic

nervous activity is established through retarded growth *in utero* and leads to raised blood pressure in later life.

TYPE II DIABETES

Insulin has a central role in fetal growth, and disorders of glucose and insulin metabolism are therefore an obvious possible link between early growth and cardiovascular disease [13]. Although obesity and a sedentary lifestyle are known to be important in the development of Type II diabetes, they seem to lead to the disease only in predisposed individuals. Family and twin studies have suggested that the predisposition is familial, but the nature of this predisposition is unknown. The disease tends to be transmitted through the maternal rather than paternal side of the family [84].

Size at birth and Type II diabetes

A number of other studies have confirmed the association between birthweight, impaired glucose tolerance and Type II diabetes first reported in Hertfordshire (Table 3) [18,29,85–88]. In the Health Professionals Study, U.S.A., the odds ratio for diabetes, after adjusting for current body mass, was 1.9 among men whose birthweights were less than 5.5 lbs (2.5 kg) compared with those who weighed 7–8.5 lbs (3.2–3.9 kg) [89]. Among the Pima Indians, U.S.A., the odds ratio for diabetes was 3.8 in men and women who weighed less than 5.5 lbs (2.5 kg) [90]. In Preston it was the thin babies who developed impaired glucose tolerance and diabetes. Lithell et al. [87] confirmed the association with thinness in Uppsala, Sweden (Table 5). The prevalence of diabetes was three times higher (relative odds by logistic regression 4.4) among men in the lowest fifth of ponderal index at birth. This was a stronger association than that with birthweight; the prevalence of diabetes being only twice as high among men in the lowest fifth of birthweight. Among the Pima Indians in the U.S.A. in whom diabetes in pregnancy is unusually common, young men and women with birth-

weights over 9.9 lbs (> 4.5 kg) had an increased prevalence of Type II diabetes [90]. The association between birthweight and Type II diabetes was therefore U-shaped. The increased risk of diabetes among babies with high birthweights was associated with maternal diabetes in pregnancy.

Insulin resistance

Both deficiency in insulin production and insulin resistance are thought to be important in the pathogenesis of Type II diabetes [91]. There is evidence that both may be determined in fetal life. Men and women with low birthweight have a high prevalence of the 'insulin resistance syndrome' [92], in which impaired glucose tolerance, hypertension and raised serum triacylglycerol concentrations occur in the same patient. The patients are insulin resistant and have hyperinsulinaemia. Table 6 shows results for a sample of the men in Hertfordshire. Phillips et al. [93] carried out insulin tolerance tests on 103 men and women in Preston. At each body mass, insulin resistance was greater in people who had a low ponderal index at birth. Conversely, at each ponderal index, resistance was greater in those with high body mass. The greatest mean resistance was therefore in those with low ponderal index at birth but high current body mass.

A recent study in San Antonio, Texas, confirmed the association between low birthweight and insulin resistance in a different ethnic group. In 30-year-old Mexican-Americans and non-Hispanic white people, those with lower birthweight had a higher prevalence of the insulin resistance syndrome [94]. Among men and women in the lowest third of the birthweight distribution and the highest third of current body mass, 25% had the syndrome. In contrast, none of the people in the highest third of birthweight and lowest third of current body mass had the syndrome. A study of young adults in the city of Haguenu, France, showed that those who had had intrauterine growth retardation had raised plasma insulin concentrations when fasting and after a standard

Table 5 Prevalence of Type II diabetes by ponderal index at birth among 60-year-old men in Uppsala, Sweden

Dashes are used in column one to indicate that the end of the range of values can be inferred from the first value in the following category.

Ponderal index at birth (kg/m ³)	No. of men	Prevalence of diabetes (%)
< 24.2	193	11.9
24.2–	193	5.2
25.9–	196	3.6
27.4–	188	4.3
≥ 29.4	201	3.5
All	971	5.7
<i>P</i> value for trend		0.001

Table 6 Prevalence of the insulin resistance syndrome in men aged 59 to 70 years according to birthweight

Dashes are used in column one to indicate that the beginning of the range of values can be inferred from the last value in the preceding category.

Birthweight, lb (kg)	No. of men	% with insulin resistance syndrome	Odds ratio adjusted for body mass index (95% confidence interval)
≤ 5.5 (2.50)	20	30	18 (2.6 to 118)
–6.5 (2.95)	54	19	8.4 (1.5 to 49)
–7.5 (3.41)	114	17	8.5 (1.5 to 46)
–8.5 (3.86)	123	12	4.9 (0.9 to 27)
–9.5 (4.31)	64	6	2.2 (0.3 to 14)
> 9.5 (4.31)	32	6	1.0
All	407	14	

glucose challenge [95]. They did not show any of the other abnormalities that occur in the insulin resistance syndrome. An interpretation of this is that insulin resistance is a primary abnormality to which other changes are secondary. A recent study of men and women who were *in utero* during the Dutch famine provides direct evidence that fetal undernutrition can programme insulin resistance and Type II diabetes [96]. Men and women exposed to famine *in utero* had higher 2-h plasma glucose concentrations than those born before or conceived after the famine. They also had higher fasting proinsulin and 2-h plasma insulin concentrations, suggesting insulin resistance.

Law [96a] reported associations between thinness at birth and raised 30-min plasma glucose concentrations in 7-year-old children in Salisbury, U.K. Whincup et al. [97] studied an older group of British children, aged 10–11 years, and found that those who had lower birthweight had raised plasma insulin concentrations, both fasting and after oral glucose. This is consistent with the association between low birthweight and insulin resistance. Among these children, however, the plasma glucose concentrations of those who had low birthweight were unaltered, which implies that despite being insulin resistant they were able to maintain glucose homeostasis. In contrast, Yajnik et al. [98] found that 4-year-old Indian children who had low birthweight had raised plasma glucose and insulin concentrations, suggesting that at the levels of poor fetal growth and insulin resistance which prevail in India even young children are unable to maintain glucose homeostasis. Forrester et al. [99] found an association between stunting at birth and reduced glucose tolerance among children in Jamaica, in whom the serum glycated haemoglobin levels rose progressively between those who were 52 cm (20.5 in) or more in length at birth and those who were 46 cm (18.1 in) or less. These findings in children provide further support for the hypothesis that Type II diabetes originates from impaired development *in utero* and that

the seeds of diabetes in the next generation have already been sown and are apparent in today's children.

Mechanisms

The processes that link thinness at birth with insulin resistance in adult life are not known. Babies born at term with a low ponderal index have a reduced mid-arm circumference, which implies that they have a low muscle bulk as well as less subcutaneous fat [100]. It is therefore possible that thinness at birth is associated with abnormalities in muscle structure and function which develop in mid-gestation and persist into adult life, interfering with insulin's ability to promote glucose uptake. Magnetic resonance spectroscopy studies show that people who were thin at birth have lower rates of glycolysis and glycolytic ATP production during exercise [101]. In response to undernutrition a fetus may reduce its metabolic dependence on glucose and increase oxidation of other substrates, including amino acids and lactate (Figure 1). This has led to the hypothesis that a glucose-sparing metabolism persists into adult life, and that insulin resistance arises as a consequence of similar processes, possibly because of reduced rates of glucose oxidation in insulin-sensitive peripheral tissues.

When the availability of nutrients to the fetus is restricted concentrations of anabolic hormones, including insulin and IGF-1, fall, while catabolic hormones, including glucocorticoids, rise (Figure 1). Persisting hormonal changes could underlie the development of insulin resistance. Bjorntorp [102] has postulated that glucocorticoids, growth hormone and sex steroids may play a major role in the evolution of the metabolic syndrome.

Recent advances in assay methodology make it possible to measure specifically plasma concentrations of the precursor of insulin: 32–33 split proinsulin [103,104]. Higher concentrations are found in people who had low birthweight and low weight at 1 year [29]. The significance of raised plasma split proinsulin concentrations

remains unclear but they are thought to indicate both insulin resistance and pancreatic β -cell dysfunction.

Insulin deficiency

Infants who are small for dates have fewer β -cells [105]. There are conflicting reports on whether the β -cell mass is reduced in patients with Type II diabetes [106]. As a working hypothesis it seems reasonable to propose that nutritional and other factors determining fetal and infant growth influence the size and function of the adult pancreatic β -cell complement. Whether and when Type II diabetes supervenes will be determined by the rate of attrition of β -cells with ageing, and by the development of insulin resistance, of which obesity is an important determinant [107].

In a sample of 103 of the men and women who took part in the Preston study, Phillips et al. [108] measured insulin secretion after intravenous infusion of glucose. The insulin response was not related to birthweight or other measurements at birth. This argues against a link between reduced fetal growth and insulin deficiency in adult life. Similarly, a study of men in Stockholm found no association between birthweight and insulin responses to infused glucose [109]. Birth length and other measures of birth size were not available in that study. There was, however, an association between short stature and a low insulin response. It is possible that insulin resistance in adult life changes insulin secretion and obscures associations with fetal growth. Studies of younger people may resolve this – a study of men aged 21 years by Robinson et al. [110] showed that those with lower birthweight had reduced plasma insulin concentrations at 30 min. Another study of men of similar age showed that a low insulin response to glucose was associated with a high placental weight and a high ratio of placental weight to birthweight. This study also confirmed the association between low insulin secretion and short stature [111]. In contrast, a study of young Pima Indians showed that those with low birthweight had evidence of insulin resistance but no defect in insulin secretion [112].

In Mysore, South India, men and women with Type II diabetes showed signs of both insulin resistance and insulin deficiency [113]. The high prevalence of insulin resistance, central obesity and Type II diabetes in people from South India living in Britain has been discussed [114,115]. The study of men and women in Mysore again showed this. Those who had Type II diabetes, however, also had a low insulin increment after a standard challenge, indicating that they were insulin deficient as well as resistant. While insulin resistance was associated with low birthweight, Type II diabetes was associated with stunting at birth in relation to birthweight, that is a high ponderal index, and with maternal adiposity.

These findings led to a novel explanation for the epidemic of Type II diabetes in urban and migrant Indian

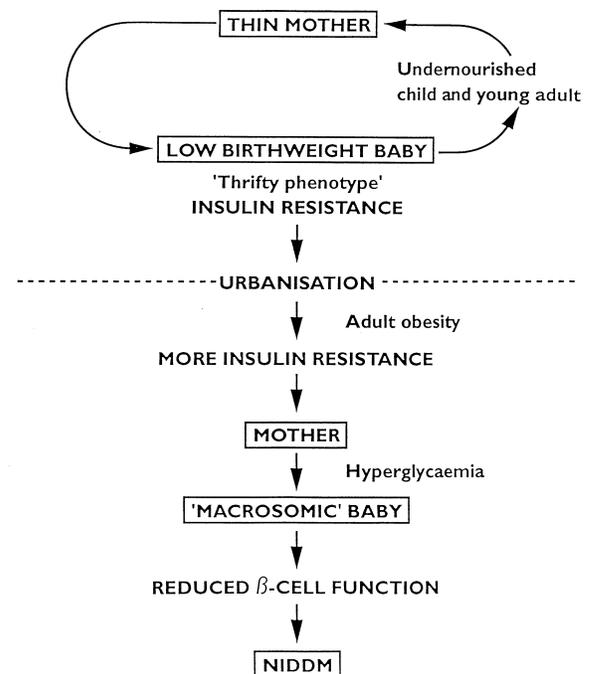


Figure 3 A model to explain the epidemic of Type II diabetes in urban India

NIDDM, non-insulin-dependent (Type II) diabetes mellitus.

populations [113] (Figure 3). Widespread fetal under-nutrition predisposes the Indian population to insulin resistance. On moving to cities, people's levels of physical activity diminish. Young women, no longer required to do agricultural work, or walk long distances to fetch water and firewood, become fatter and therefore more insulin resistant. They are therefore unable to maintain glucose homeostasis during pregnancy, even at relatively low levels of obesity, and become hyperglycaemic, though not necessarily diabetic. It is known that high plasma glucose concentrations within the normal range influence fetal growth and lead to macrosomia [116].

Serum cholesterol and blood clotting

Studies in Sheffield, U.K., show that the neonate that has a short body and low birthweight in relation to the size of its head, although within the normal range of birthweight, has persisting disturbances of cholesterol metabolism and blood coagulation [117–119]. Disproportion in body length relative to head size is thought to result from undernutrition in late gestation. The fetus diverts oxygenated blood away from the trunk to sustain the brain. This affects the growth of the liver, two of whose functions, regulation of cholesterol and of blood clotting, seem to be permanently perturbed. Disturbance of cholesterol metabolism and blood clotting are both important features of coronary heart disease.

The Sheffield records included abdominal circumference at birth, as well as length, and it was specifically

Table 7 Mean serum cholesterol concentrations according to abdominal circumference at birth in men and women aged 50–53 years

Dashes are used in column one to indicate that the beginning of the range of values can be inferred from the last value in the preceding category.

Abdominal circumference, inches (cm)	No. of people	Total cholesterol (mmol/l)	Low-density lipoprotein cholesterol (mmol/l)
≤ 11.5 (29.2)	53	6.7	4.5
–12.0 (30.5)	43	6.9	4.6
–12.5 (31.8)	31	6.8	4.4
–13.0 (33.0)	45	6.2	4.0
> 13.0 (33.0)	45	6.1	4.0
All	217	6.5	4.3

reduction in this birth measurement that predicted raised serum low-density lipoprotein cholesterol and plasma fibrinogen concentrations in adult life [117,118]. The differences in concentrations across the range of abdominal circumference values were large (Table 7), statistically equivalent to 30% differences in mortality caused by coronary heart disease. The findings for plasma fibrinogen concentrations, a measure of blood coagulability, were of similar magnitude.

Since both cholesterol and fibrinogen metabolism are regulated by the liver, one interpretation of these findings is that reduced abdominal circumference at birth reflects impaired liver growth and consequent re-programming of liver metabolism. Further understanding of liver programming may come more rapidly from animal than from human studies. Experiments on rats have shown that undernutrition *in utero* can permanently alter the balance of two liver enzymes, phosphoenolpyruvate carboxykinase and glucokinase, which are involved respectively in the synthesis and breakdown of glucose [120]. A low protein diet during gestation permanently changes the balance of enzyme activity in the offspring in favour of synthesis. It is thought that this reflects enhancement of cell replication in the area around the portal vein, which carries blood from the gut to the liver, at the expense of the cells around the hepatic vein. These experiments are of particular interest because they show that undernutrition after birth has no effect, and because the two enzymes are not normally synthesized until after birth, which suggests that their production can be regulated before the genes encoding them are transcribed.

SUMMARY

Associations between low birthweight and coronary heart disease, raised blood pressure and Type II diabetes have been repeatedly demonstrated. There is less information about stroke. Relatively few studies have had access to measurements of birth size other than weight. This is a major limitation because birthweight is a crude

summary index of growth, and because blood pressure and glucose/insulin metabolism can be programmed by nutritional influences that do not alter birthweight. Studies which do include birth length as well as weight consistently suggest that thinness at birth is associated with the development of insulin resistance. Other associations, for example, those with blood pressure, are less consistent. One interpretation of this is that blood pressure can be programmed at various stages of gestation while insulin resistance is programmed in late gestation, when disproportionate fetal growth is manifest. This is, however, an uncertain inference and is not borne out by the Dutch famine study, in which reduced glucose tolerance was associated with exposure to famine at any stage of gestation. Associations between placental size and later disease differ between studies. In animals, placental responses to undernutrition depend on the mother's nutritional state before pregnancy, but we have little information about this in humans. It is, however, apparent that placental growth and function are one of the influences which programme the fetus, and that this occurs without the placenta being clinically abnormal.

THE FUTURE

If we are to be able to use the information outlined here to prevent disease we need to progress beyond epidemiological associations to greater understanding of the cellular and molecular processes that underlie them. We need to know what factors limit the delivery of nutrients and oxygen to the human fetus; how the fetus adapts to a limited supply; how these adaptations programme the structure and physiology of the body; and by what molecular mechanisms nutrients and hormones alter gene expression. Further research requires a strategy of interdependent clinical, animal and epidemiological studies.

As yet, we do not know the true impact of maternal nutrition on fetal development. The relatively disappointing effects of nutritional interventions in pregnancy on fetal growth in humans have led to the view that fetal

development is little affected by changes in maternal nutrition, except in circumstances of famine. It is, however, clear that birthweight alone is an inadequate summary measure of fetal growth, and that we need a more sophisticated view of optimal fetal development which takes into account the long-term sequelae of fetal adaptations to undernutrition.

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