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The effect of nutrition of the fetus and neonate on cardiovascular disease in adult life

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The present paper presents evidence that restraint of growth and development during critical periods of fetal life and infancy has an important effect on the development of cardiovascular disease (CVD).

GEOGRAPHICAL STUDIES

Early evidence that long-term effects of an adverse environment in fetal life and infancy may be determinants of CVD in humans came from geographical studies. The large geographical differences in death rates from CVD in England and Wales remain largely unexplained. Variations in adult diet and cigarette smoking do not explain why the highest rates are in industrial areas in the north and west of the country, and in some of the less affluent rural areas such as North Wales. Rates are low throughout the south and east, including London.

One possible explanation is that the causes of the geographical differences begin to operate not in adult life but during childhood. The existence of detailed records of infant mortality from the beginning of the century allows current death rates in any area of England and Wales to be compared with infant mortality rates 60 years or more ago. This comparison can be made with the country divided into 212 local authority groupings. The correlation between past infant mortality and current mortality from CVD is remarkably strong, the correlation coefficient being 0·73 (Barker & Osmond, 1986). Infant mortality is, of course, no more than a general indicator of an adverse environment. But such a strong relationship is, at the very least, suggestive that some aspects of poor living conditions in childhood determine risk of CVD in adult life. This conclusion was first put forward by Forsdahl (1977), who found a similar geographical relationship between infant and cardiovascular mortality in the twenty counties of Norway.

The detailed infant mortality records in England and Wales make it possible to refine this general conclusion. The records distinguish neonatal mortality (deaths before 1 month of age) from post-neonatal mortality (deaths from 1 month to 1 year). They reveal the new, and perhaps surprising, clue that cardiovascular mortality in adults is more closely linked to neonatal mortality than to post-neonatal mortality (Barker *et al.* 1989*b*).

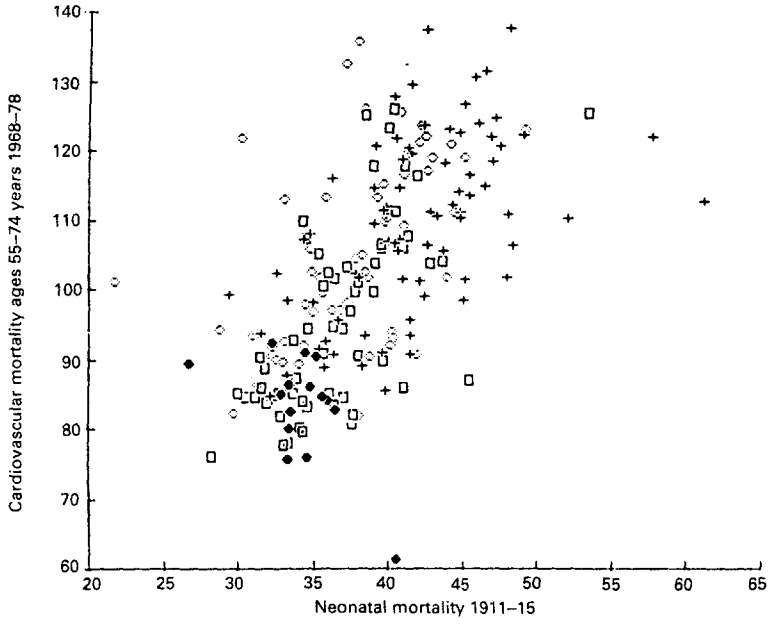

Fig. 1. Cardiovascular and neonatal mortality in England and Wales. (◇), Urban districts; (□), rural districts; (+), county boroughs; (◆), London boroughs.

This relationship is shown in Fig. 1. In the past neonatal mortality was high in places where many babies had a low birth weight (Local Government Board, 1910). High neonatal mortality was generally associated with high maternal mortality rates, which were found in places where women had poor physique and health (Campbell *et al.* 1932). There is, therefore, a geographical association between poor maternal physique and health, poor fetal growth and high death rates from CVD. This geographical association is reinforced by studies of migrants. A study of 2 million people who died in England and Wales during 1969–72 showed that the increased risk of ischaemic heart disease (IHD) and stroke among people born in northern England and in Wales persisted whether or not they moved to other parts of the country (Osmond *et al.* 1990).

The recent fall in stroke mortality in many Western countries is consistent with improvement in maternal health during the past century. To explain the rise in IHD it seems necessary to postulate two groups of causes, one associated with poor living standards and the other associated with prosperity and linked, presumably, to the high-energy Western diet.

ANIMAL STUDIES

Ideas about the importance of long-term effects of interference with early growth, so-called 'programming', in determining risk of disease in adulthood are reinforced by studies in animals. Transient events in prenatal or early postnatal life have permanent and profound effects on physiology although such effects may remain latent until the animal is mature. One example of this comes from experiments in which the nutrition of pregnant and lactating rats was manipulated. The adult body size of the offspring was more powerfully determined by their mothers' nutrition during pregnancy and lactation than by their genetic constitution (Dubos *et al.* 1966). Undernutrition during pregnancy

stunted the growth of the offspring and this effect could not be reversed by an optimal diet after birth (Blackwell *et al.* 1968).

Nutritional deprivation in early life affects the size and DNA content of different organ systems depending on the precise time at which it occurs. In rats, a brief period of energy restriction immediately postnatally causes a profound reduction in the weight of the liver, spleen and thymus, while brain and skeletal muscle are spared (Winick & Noble, 1966). Energy restriction immediately after weaning reduced only the weight of the thymus.

The metabolic activities of rate-limiting enzymes that control cholesterol synthesis seem to be especially sensitive to the content of the diet in infancy. The early nutrition of rats has been shown to determine the response to a dietary fat challenge in adult life (Coates *et al.* 1983) and, in baboons, serum concentration and biliary secretion of cholesterol are strongly influenced by the type of diet that they were fed in the neonatal period (Mott *et al.* 1991).

STUDIES IN HUMANS

Whether these demonstrations of the programming effect of the early environment are applicable to the pathogenesis of CVD in humans can be explored by studying adults in middle and old age whose growth and development in infancy was recorded. From 1911 onwards, every baby born in the county of Hertfordshire was weighed at birth, visited periodically by a health visitor throughout the first year and weighed again at 1 year of age. The records of these visits have survived so that it is possible to trace men and women born 60 and more years ago and to relate these measurements to the later occurrence of illness and death and to the level of known risk factors for CVD (Barker *et al.* 1989*c*).

In an early study 6500 men who were born in eight districts of the county between 1911 and 1930 were followed up. Table 1 shows standardized mortality ratios for IHD in the men, of whom 469 had died from the disease. The ratios fall steeply with increasing weight at 1 year, a trend not shown by deaths from non-circulatory causes. IHD mortality also falls with increasing birth weight, although the relationship is not as strong as with weight at 1 year. Stroke mortality shows similar trends. An interpretation of these findings is that programming of CVD occurs both during fetal life and during infancy.

Table 1. *Standardized mortality ratios for ischaemic heart disease (IHD) according to weight at 1 year old in 6500 men born during 1911–30*

(No. of deaths is shown in parentheses)

Weight at 1 year old (lbs)	Ischaemic heart disease	All non-circulatory disease
≤18	100 (36)	74 (39)
–20	84 (90)	99 (157)
–22	92 (180)	74 (215)
–24	70 (109)	67 (155)
–26	55 (44)	84 (99)
≥27	34 (10)	72 (31)
All	78 (469)	78 (696)

Table 2. *Mean plasma fibrinogen in men aged 59–70 years*

Weight at 1 year old (lbs)	No. of men	Fibrinogen (g/l)*
≤18	37	3·21
–20	91	3·10
–22	177	3·13
–24	173	2·97
–26	80	2·93
≥27	33	2·93
All: Mean	591	3·04
SD		0·59

* Geometric mean values adjusted for age.

These findings prompt questions about mechanism. There is now evidence that haemostatic variables, glucose tolerance, blood pressure and lipid metabolism are all susceptible to the programming effects of the environment in early life. Detailed description of the associations between these variables and growth in fetal and infant life is beyond the scope of the present paper. Instead, chosen examples that illustrate general points are presented.

High plasma concentration of fibrinogen is a strong predictor of increased risk of both IHD and stroke (Meade & North, 1977; Meade *et al.* 1986). Fibrinogen concentrations have been measured in 591 men aged 59–70 years still living in Hertfordshire (Barker *et al.* 1992). Table 2 shows that concentrations fell as weight at 1 year of age increased ($P<0·001$). The difference in mean fibrinogen levels between men who weighed 18 pounds or less at 1 year and those who weighed 27 pounds or more was large. It was statistically equivalent to a difference in cardiovascular mortality of about 40%. The trends in plasma fibrinogen with weight at 1 year were independent of age, smoking, alcohol intake and obesity. Simultaneous analysis of plasma fibrinogen with smoking and weight at 1 year showed that the effects of smoking add to those associated with failure of infant growth.

Plasma levels of another haemostatic factor, Factor VII, a similarly strong and independent predictor of cardiovascular mortality, showed trends similar to those of plasma fibrinogen. Whereas fibrinogen is an acute phase protein, and rises in response to a number of stimuli, Factor VII is a key component of the intrinsic coagulation system. Neither plasma fibrinogen nor Factor VII levels were related to birth weight. Circulating fibrinogen and Factor VII concentrations are largely regulated by the liver. The high adult levels associated with reduced infant growth may be a persisting response to impaired liver development during a critical early phase.

Standard 75 g oral glucose tolerance tests have been carried out on 370 of the men in Hertfordshire (Hales *et al.* 1991). The percentage of men with impaired glucose tolerance, (2 h plasma glucose 7·8–11·0 mmol/l) or diabetes (2 h glucose 11·1 mmol/l and over) fell progressively up to the highest values of birth weight and weight at 1 year (Table 3). There were threefold differences in the prevalence of impaired glucose tolerance and diabetes between men with the lowest and highest early weights. These trends were independent of body mass index. Table 4 shows how infant growth protects against the deleterious effect of higher body mass in adult life; and, conversely, how

Table 3. *Percentage of men aged 59–70 years with impaired glucose tolerance or diabetes according to weight at 1 year old*

Wt at 1 year old (lbs)	No. of men	2 h glucose (mmol/l)			Odds ratio*	
		7·8–11·0	≥11·1	≥7·8		95% CI
≤18	23	26	17	43	8·2	1·8–38
–20	63	21	11	32	4·8	1·2–19
–22	107	22	7	30	4·2	1·1–16
–24	105	13	5	18	2·1	0·5– 7·9
–26	48	13	6	19	2·1	0·5– 9·0
≥27	24	13	0	13	1·0	
Total	370	18	7	25		

CI, confidence interval.

* Odds ratio for 2 h glucose ≥7·8 mmol/l, adjusted for body mass index, χ^2 for trend 14·9, $P<0·01$.

Table 4. *Mean plasma glucose (mmol/l) 2 h after 75 g oral glucose in men aged 59–70 years according to weight at 1 year old*

(No. of men is shown in parentheses)

	Plasma glucose (mmol/l)*			
Wt at 1 year old (lbs) . . .	–21·5	–23·5	>23·5	
Adult body mass index (kg/m^2)				Total
–25·4	6·6	6·1	5·8	6·2
	(45)	(39)	(36)	(120)
–28	6·7	6·9	5·9	6·5
	(47)	(44)	(36)	(127)
>28	7·7	7·4	6·6	7·2
	(39)	(43)	(41)	(123)
Total	7·0	6·8	6·1	6·6
	(131)	(126)	(113)	(370)

* Geometric standard deviation of plasma glucose 1·4.

lower body mass protects against the deleterious effect of reduced early growth. Of the men whose birth weights and weights at 1 year old were below the median, and whose body mass indices were above the median, 27% had impaired glucose tolerance and a further 15% had diabetes. Only 5% of the men who were above the median for early weight and below the median for body mass index had impaired tolerance and only a further 2% had diabetes.

Concentrations of plasma 32–33 split proinsulin were also higher in men with lower birth weight and weight at 1 year old. Raised concentrations of this insulin precursor may indicate production of insulin by a relatively small complement of pancreatic β cells. It is known that much of the growth of the islets of Langerhans in the pancreas is completed around the time of birth. The findings suggest that factors which reduce fetal and infant

Table 5. *Mean systolic pressure in men aged 59–70 years according to birth weight*

Birth wt (lbs)	No. of men	Mean systolic pressure (mm Hg)
≤5·5	31	169
–6·5	94	166
–7·5	250	165
–8·5	231	163
–9·5	123	163
>9·5	56	162
All: Mean	785	164
SD		23

growth impair pancreatic development and limit the size and function of the adult pancreatic β cell complement.

Of the men in Hertfordshire 95% were breast-fed and 20% were still receiving breast milk at 1 year. These men had high death rates from IHD, with standardized mortality ratios of 97 compared with 77 in the remainder. They also had elevated levels of serum low-density-lipoprotein-cholesterol, 5·0 *v.* 4·6 mmol/l, and of apolipoprotein B, 1·14 *v.* 1·08 g/l (Fall *et al.* 1992). The explanation of these findings is unclear but they suggest that, in keeping with the observations in animals (Coates *et al.* 1983; Mott *et al.* 1991), feeding practices in infancy can modify lipid metabolism in adult life.

The inverse relationship between systolic blood pressure and birth weight present in the Hertfordshire men is shown in Table 5. A similar relationship has also been found in a national sample of men and women at the age of 36 years (Barker *et al.* 1989*a*). In contrast to plasma concentrations of haemostatic factors and rates of glucose intolerance, blood pressure is not related to weight at 1 year independently of birth weight. This suggests that the critical period when blood pressure is sensitive to programming may be largely restricted to fetal life rather than extending throughout infancy.

Birth weight is a summary measure of fetal growth; it comprises head size, body length and the amount of fat that the baby has stored. To explore the relationship between different aspects of fetal growth and adult blood pressure in greater detail, a group of men and women now aged about 50 years were studied (Barker *et al.* 1990). They were born in a hospital in Preston, England, where unusually detailed observations were made on newborn babies. Table 6 shows the mean systolic pressures according to placental weight and birth weight in the 449 men and women. These two variables act in opposite directions; blood pressure falls by about 10 mm Hg from the lowest to the highest groups of birth weight but rises by about 12 mm Hg from the lowest to the highest groups of placental weight. The highest blood pressures are in men and women who were small babies with large placentas. Adjusting for gestational age, current body mass index and alcohol consumption did not affect these trends.

Large placental weight was also associated with clinical hypertension in adult life. Among the 449 men and women the risk of being under treatment for hypertension was 3·7 times higher in those with placentas weighing more than 1·5 lbs than among those whose placentas weighed less than 1·0 lb.

In a survey of blood pressure in 405 4-year-old children in Salisbury, England, the

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Table 6. *Mean systolic pressures (mm Hg) of men and women aged 46–54 years according to birth weight and placental weight*

(No. of subjects is shown in parentheses)

Birth wt (lbs)	Placental wt (lbs)				
	–1·0	–1·25	–1·5	>1·5	All
≤5·5	152	154	153	206	154
	(26)	(13)	(5)	(1)	(45)
–6·5	147	151	150	166	151
	(16)	(54)	(28)	(8)	(106)
–7·5	144	148	145	160	149
	(20)	(77)	(45)	(27)	(169)
>7·5	133	148	147	154	149
	(6)	(27)	(42)	(54)	(129)
All	147	149	147	157	150
	(68)	(171)	(120)	(90)	(449)

findings were similar to those in adults. Systolic pressure was inversely related to birth weight and positively related to placental weight (Law *et al.* 1991).

It is worth emphasizing that most of the people in Preston who had high systolic blood pressure were not especially small at birth. Their birth weights were within the normal range but their placentas were large. An interesting feature of these babies with the heaviest placentas is that their bodies were disproportionately short in relation to their head circumference. It is known that a fetal reflex response to hypoxia results in blood being preferentially diverted to the head at the expense of depriving other tissues of blood flow (Thornberg, 1991). It is possible that disproportionate shortness at birth is a consequence of a sustained response of this kind. There are a number of possible mechanisms whereby circulatory changes in the fetus could lead to permanent changes in the structure of blood vessels in adults (Folkow, 1982).

The causes of low birth weight in relation to placental weight are not well understood. But, in Preston, only 7% of babies born at term to mothers in social classes I and II had placentas that weighed more than 1·5 lbs; this compares with 24% for mothers in lower social classes. One factor linking low social class with large placental weight may be poor nutrition. Evidence in support comes from a recent study of 8684 births in Oxford that shows an association between iron-deficiency anaemia and increased placental weight (Godfrey *et al.* 1991).

The findings described here have implications both for the pathogenesis of CVD and for maternal and infant health. The relationships between early growth and risk factors and rates of disease are continuous. Plasma levels of fibrinogen (Table 2), the prevalence of impaired glucose tolerance (Table 3), and levels of systolic blood pressure (Table 5) fall progressively up to the highest values of weight at 1 year or birth weight. If the criterion for successful fetal and infant growth is adult health and longevity, we may no longer be entitled to assume that a baby of average birth weight and weight in infancy has necessarily achieved its optimum weight.

Studies on the relationship between early growth and adult obstructive airways disease have proceeded in parallel with those on CVD. There is now strong evidence that obstructive airways disease is associated with retarded growth during the period of rapid

lung development in fetal life and infancy, and with acute respiratory infection during infancy (Barker *et al.* 1991).

CONCLUSION

The results of these studies show that retarded growth in fetal life and infancy is strongly related both to mortality from CVD and to adult levels of some of its known risk factors. Any argument concerns the extent to which this relationship should be interpreted as being causal. In broad terms there are three possible explanations for our findings. The first is that people born into an adverse environment tend to remain in one, and lower birth weight and weight at 1 year of age are merely markers for adverse environmental influences that act throughout life. Although this interpretation can just be sustained if the ecological data are viewed in isolation, it cannot account for the results of follow-up studies of individuals. In Hertfordshire birth weight was not associated with social class, either at birth or currently. Plasma fibrinogen, Factor VII, glucose, insulin, proinsulin or blood pressure were not related to social class (Hales *et al.* 1991; Barker *et al.* 1992) and their associations with early growth were seen within each social class. If a poor early environment caused higher levels of cardiovascular risk factors through the cumulative effect of a variety of adverse influences acting during childhood and adolescence, one would expect these higher levels of risk factors to be associated with shorter adult stature. Blood pressure levels in Hertfordshire men were not associated with adult height and the weak associations of plasma fibrinogen and plasma glucose with shorter stature were abolished after allowing for weight at 1 year of age.

A second possible explanation for the relationship is that genetic influences that first show themselves in early life as growth failure are revealed later in adult life through the occurrence of degenerative disease. The implication here is that the genes that determine low birth weight are the same as or are closely linked to the genes that determine CVD. This explanation is not likely to be correct because birth weight does not seem to be strongly genetically determined (Carr-Hill *et al.* 1987), nor is there much evidence that CVD has, in most people, a major genetic component.

The relationship between CVD and retarded growth in early life can be interpreted as a long-term effect on physiology and metabolism imposed by an adverse environment during critical periods of development. This conclusion does not imply that the environment in adult life is unimportant, although it may explain why the known adult risk factors predict CVD in individuals so poorly. A common origin in retarded early growth may explain why levels of one cardiovascular risk factor, for example plasma glucose concentrations, correlate with another, for example blood pressure (Hales *et al.* 1991). The different relationships between risk factors and specific patterns of retarded fetal or infant growth, as shown by fibrinogen and blood pressure, may explain why the distributions of risk factors overlap but do not coincide.

Further work on the programming of CVD is focusing on the nature and timing of environmental factors that influence the growth of the fetus and infant, and programme its structure and metabolism. Laboratory studies that allow direct manipulation of the fetal environment in experimental animals are running in parallel with studies in humans which exploit the ability of ultrasound techniques to examine maternal influences on different aspects of fetal development.

REFERENCES

Barker, D. J. P., Bull, A. R., Osmond, C. & Simmonds, S. J. (1990). Fetal and placental size and risk of hypertension in adult life. *British Medical Journal* **301,** 259–262.

Barker, D. J. P., Godfrey, K. M., Fall, C., Osmond, C., Winter, P. D. & Shaheen, S. O. (1991). Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *British Medical Journal* **303,** 671–675.

Barker, D. J. P., Meade, T. W., Fall, C. H. D., Lee, A., Osmond, C., Phipps, K. & Sterling, Y. (1992). Relation of fetal and infant growth to plasma fibrinogen and factor VII concentrations in adult life. *British Medical Journal* **304,** 148–152.

Barker, D. J. P. & Osmond, C. (1986). Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* **i,** 1077–1081.

Barker, D. J. P., Osmond, C., Golding, J., Kuh, D. & Wadsworth, M. E. J. (1989*a*). Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *British Medical Journal* **298,** 564–567.

Barker, D. J. P., Osmond, C. & Law, C. M. (1989*b*). The intrauterine and early postnatal origins of cardiovascular disease and chronic bronchitis. *Journal of Epidemiology and Community Health* **43,** 237–240.

Barker, D. J. P., Winter, P. D., Osmond, C., Margetts, B. & Simmonds, S. J. (1989*c*). Weight in infancy and death from ischaemic heart disease. *Lancet* **ii,** 577–580.

Blackwell, N. M., Blackwell, R. Q., Yu, T. T. S., Weng, Y. S. & Chow, B. F. (1968). Further studies on growth and feed utilization in progeny of underfed mother rats. *Journal of Nutrition* **97,** 79–84.

Campbell, J. M., Cameron, D. & Jones, D. M. (1932). High maternal mortality in certain areas. *Ministry of Health Reports on Public Health and Medical Subjects* no. 68. London: H.M. Stationery Office.

Carr-Hill, R., Campbell, D. M., Hall, M. H. & Meredith, A. (1987). Is birthweight determined genetically? *British Medical Journal* **295,** 687–689.

Coates, P. M., Brown, S. A., Sonaware, B. R. & Koldovsky, O. (1983). Effect of early nutrition on serum cholesterol levels in adult rats challenged with a high fat diet. *Journal of Nutrition* **113,** 1046–1050.

Dubos, R., Savage, D. & Schaedler, R. (1966). Biological Freudianism: lasting effects of early environmental influences. *Pediatrics* **38,** 789–800.

Fall, C. H. D., Barker, D. J. P., Osmond, C., Winter, P. D., Clark, P. M.S. & Hales, C. N. (1992). Relation of infant feeding to adult serum cholesterol concentration and death from ischaemic heart disease. *British Medical Journal* **304,** 801–805.

Folkow, B. (1982). Physiological aspects of primary hypertension. *Physiological Reviews* **62,** 347–504.

Forsdahl, A. (1977). Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? *British Journal of Preventive Social Medicine* **31,** 91–95.

Godfrey, K. M., Redman, C. W. G., Barker, D. J. P. & Osmond, C. (1991). The effect of maternal anaemia and iron deficiency on the ratio of fetal weight to placental weight. *British Journal of Obstetrics and Gynaecology* **98,** 886–891.

Hales, C. N., Barker, D. J. P., Clark, P. M. S., Cox, L. J., Fall, C., Osmond, C. & Winter, P. D. (1991). Fetal and infant growth and impaired glucose tolerance at age 64 years. *British Medical Journal* **303,** 1019–1022.

Law, C. M., Barker, D. J. P., Bull, A. R. & Osmond, C. (1991). Maternal and fetal influences on blood pressure. *Archives of Diseases in Childhood* **66,** 1291–1295.

Local Government Board (1910). *Thirty-ninth Annual Report* 1909–10. *Supplement on Infant and Child Mortality*. London: H.M. Stationery Office.

Meade, T. W., Mellows, S., Brozovic, M., Miller, G. J., Chakrabati, R. R., North, W. R. S., Haines, A. P., Stirling, Y., Imeson, J. D. & Thompson, S. G. (1986). Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. *Lancet* **ii,** 533–537.

Meade, T. W. & North, W. R. S. (1977). Population-based distributions of haemostatic variables. *British Medical Bulletin* **33,** 283–288.

Mott, G. E., Lewis, D. S. & McGill, H. C. (1991). Programming of cholesterol metabolism by breast or formula feeding. *The Childhood Environment and Adult Disease. Ciba Symposium* no. 156. Chichester: John Wiley.

Osmond, C., Barker, D. J. P. & Slattery, J. M. (1990). Risk of death from cardiovascular disease and chronic bronchitis determined by place of birth in England and Wales. *Journal of Epidemiology and Community Health* **44,** 139–141.

Thornberg, K. L. (1991). Fetal response to intrauterine stress. *The Childhood Environment and Adult Disease. Ciba Symposium* no. 156. Chichester: John Wiley.

Winick, M. & Noble, A. (1966). Cellular response in rats during malnutrition at various ages. *Journal of Nutrition* **89,** 300–306.

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