interpreted with extreme caution. Hypotheses generated by ecological studies need to be rigorously tested in epidemiological studies based on individuals rather than groups. These are considered in the second part of this review.[15]

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Review article

The maternal and fetal origins of cardiovascular disease

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The limited ability of known risk factors to predict the occurrence of cardiovascular disease in individuals is often forgotten.[1] Rose has pointed out that for a man falling into the lowest risk groups for plasma lipid concentrations, blood pressure, cigarette smoking, and presence of pre-existing symptoms of coronary heart disease, the commonest cause of death is coronary heart disease.[2] Nor is the paradoxical social and geographical distribution of ischaemic heart disease understood. Why is it that a disease that is associated globally with affluence is now commonest in the poorest parts of Britain and among people with the lowest incomes?

Geographical studies

A possible explanation for the geographical differences in mortality from cardiovascular disease in England and Wales is that its causes begin to operate not in adult life but during fetal development and infancy. Records of infant mortality dating from the beginning of the century allow current death rates in the 212 local authority areas of England and Wales to be compared with infant mortality rates in the same places 60 or more years ago. The correlation between past infant mortality and current mortality from cardiovascular disease ($r = 0{\cdot}73$) is strikingly close.[3] Infant mortality is, of course, no more than a general indicator of adverse environmental conditions. But such a strong relation is, at the very least, suggestive that some aspect of poor living conditions in early childhood determines risk of cardiovascular disease in adult life.

The records of infant mortality in England and Wales are sufficiently detailed to allow neonatal mortality (ie, deaths before one month of age) to be distinguished from postneonatal mortality (ie, deaths between the ages of one month and one year). A further analysis using these separate categories showed that adult cardiovascular mortality is more closely linked to neonatal mortality 60 years earlier than to postneonatal mortality.[4]

Neonatal mortality in the past was high in places where many babies were born with low birth weight.[5] Neonatal mortality is also known to have been associated with high maternal mortality. High rates for both neonatal and maternal mortality were found in places where the physique and health of women were poor.[6] Cardiovascular disease is therefore associated more strongly with poor maternal physique and health and poor fetal growth than with conditions, such as overcrowding, that predispose to high postneonatal death rates.

Animal studies

Ideas about the importance of early life in determining risk of disease in adulthood are reinforced by studies in animals. Transient events

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in prenatal or early postnatal life have permanent and profound effects on physiology though such effects may remain latent until the animal is mature. A female rat injected with a few micrograms of testosterone propionate during the first four days of life develops normally until puberty. Only then does it become apparent that the hypothalamic neuronal substrate that mediates the cyclic release of gonadotrophins has been irreversibly altered to a male pattern when, despite adequate ovarian and pituitary function, the animal fails to ovulate or show normal patterns of female sexual behaviour.[7] The same injection of androgen given when the animal is 10 days old has no effect on reproductive function. An example more directly relevant to the theme of this paper is provided by the results of experiments in which the nutrition of pregnant and lactating rats was manipulated. The adult body size of these rats was more powefully determined by their mothers' nutrition during pregnancy and lactation than by their genetic constitution[8]. Undernutrition during pregnancy stunted the growth of the offspring and this effect could not be reversed by an optimal diet after birth.[9]

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 after birth caused a profound reduction in the weight of the liver, spleen, and thymus, while brain and skeletal muscle were spared.[10] Energy restriction immediately after weaning reduced only the weight of the thymus.

The metabolic activity of rate limiting enzymes that control cholesterol synthesis seems 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[11] 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.[12]

Studies in humans

Whether these ideas about the programming effect of the early environment are applicable to the pathogenesis of cardiovascular disease 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 one year of age. The records of these visits have survived so that it is possible to trace men and women born about 60 years ago and to relate these measurements to the later occurrence of illness and death and to the level of known risk factors for cardiovascular disease.

In the first study, 6500 men born in eight districts of the county between 1911 and 1930 were followed up.[13] Table I shows their standardised mortality ratios for ischaemic heart disease according to weight at one year; the ratios fall steeply as weight at one year increases. There are similar trends with increasing birthweight, though the relation is not as strong as with weight at one year.

Table I Standardised mortality ratios for ischaemic heart disease according to weight at one year in 6500 men born during 1911–30. Numbers of deaths in parentheses

Weight at one year (pounds)	*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)

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.[14–18] Detailed description of the associations between these variables and growth in fetal and infant life is beyond the scope of this paper. Instead, we have chosen examples that illustrate general points.

High plasma concentration of fibrinogen is a strong predictor of increased risk of both ischaemic heart disease and stroke.[19 20] Fibrinogen concentrations have been measured in 591 men aged 59 to 70 years still living in Hertfordshire.[14] Table II shows that concentrations are inversely related to weight at one year of age. Fibrinogen concentrations are not related to birthweight and only weakly related to adult height. In a simultaneous regression with weight at one year, the effect of adult height is no longer apparent. Cigarette smoking, as expected, was also associated with increased plasma levels of fibrinogen but the relation with weight at one year was not diminished by adjustment for cigarette smoking.

Table II Mean plasma fibrinogen in men aged 59 to 70 years

Weight at one year (pounds)	*Number of men*	*Fibrinogen (g/litre)**
≤18	37	3·21
−20	91	3·08
−22	177	3·14
−24	173	2·98
−26	80	2·95
≥27	33	2·93
All	591	3·05

*Geometric mean values adjusted for age and cigarette smoking

Glucose tolerance tests have been carried out on 370 of these men.[15] The percentage of men with impaired glucose tolerance, defined by a plasma glucose concentration of 7·8 mmol/litre or more at two hours, falls progressively with both increasing birthweight and weight at one year (table III). There are threefold differences in the prevalence of impaired glucose tolerance and diabetes between men with the highest and lowest early weights. Concentrations of plasma 32–33 split proinsulin are also inversely related to weight at one year. Raised concentrations of this insulin precursor are thought to be an indicator of pancreatic β cell dysfunction. These findings suggest that factors which retard fetal and infant growth impair pancreatic development and limit the eventual size or function of the adult pancreatic β cell complement.

Table III Impaired glucose tolerance (2 h glucose ≥7·8 mmol/litre) in men aged 59 to 70 years

Weight at one year (pounds)	Number of men	Impaired glucose tolerance No	%	Odds ratio adjusted for body mass index (95% C I)
≤18	23	10	43	8·2 (1·8 to 38)
−20	63	20	32	4·8 (1·2 to 19)
−22	107	32	30	4·2 (1·1 to 16)
−24	105	19	18	2·1 (0·5 to 7·9)
−26	48	9	19	2·1 (0·5 to 9·0)
≥27	24	3	13	1·0
Total	370	93	25	χ^2 for trend = 14·9 ($p < 0·001$)

The inverse relation between systolic blood pressure and birthweight present in the Hertfordshire men is shown in table IV. A similar relation has also been found in a national sample of men and women at the age of 36 years.[21] In contrast to plasma concentrations of fibrinogen and rates of glucose intolerance, blood pressure in these men is not related to weight at one year independently of birthweight, nor is it related to adult height. This may indicate that the critical period when blood pressure is sensitive to programming is during fetal life rather than infancy.

These discoveries have implications both for the pathogenesis of cardiovascular and other diseases, and also for maternal and infant health. The relations between early growth and risk factors and rates of disease are continuous. Plasma levels of fibrinogen (table II), the prevalance of impaired glucose tolerance (table III), and levels of systolic blood pressure (table IV) fall progressively up to the highest values of weight at one year or birthweight. 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 birthweight and weight in infancy has necessarily achieved its optimum weight.

Birthweight is a summary measure of fetal growth; it mixes up head size, body length, and the amount of fat that the baby has stored. To explore the relation between different aspects of fetal growth and adult blood pressure in greater detail, we examined 449 men and women now aged around 50 years who had been born in Sharoe Green hospital in Preston[16] where unusually detailed observations were made on newborn babies. Table V shows the mean systolic pressures according to placental weight and birth weight. These two variables act in opposite directions; blood pressure falls by around 10 mm Hg from the lowest to the highest groups of birthweight but rises by around 12 mm Hg from the lowest to the highest groups of placental weight. 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 these 449 men and women the rate of being under treatment for hypertension was 3·7 times higher in those with placentas weighing more than 1·5 lb (680 g) than among those whose placentas weighed less than 1·0 lb (450 g). A recent survey of the blood pressures of 405 four year old children showed the same opposing association with birthweight and placental weight as was found in the 50 year old men and women.[22]

Table IV Mean systolic blood pressure in men aged 59 to 70 years

Birthweight (pounds)	Number of men	Systolic pressure
−5·5	31	169
−6·5	95	166
−7·5	251	165
−8·5	233	163
−9·5	125	162
>9·5	56	162
All	791	164

Table V Mean systolic pressures (mm Hg) of men and women aged 46 to 54 years according to birthweight and placental weight. Numbers of people in parentheses

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

It is worth emphasising that most of the people in Preston who had high systolic blood pressure were not especially small at birth. Their birthweights 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. In animals it is known that a fetal response to hypoxia results in blood being preferentially diverted to the brain and myocardium at the expense of depriving other tissues of blood flow.[23] It is not too far fetched to speculate that the pattern of fetal growth described above is the result of a similar mechanism operating in humans.

The causes of a disproportionately large placenta 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 lb. 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.[24]

Studies on the relation between early growth and adult obstructive airways disease have proceeded in parallel with those on cardiovascular disease. 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.[25]

Conclusions

The results of these studies show that retarded growth in fetal life and infancy is strongly related both to mortality from cardiovascular disease and to adult levels of some of its known risk factors. Any argument concerns the extent to which this relation should be interpreted as being causal. In broad terms there are three possible explanations for our findings. The first is that birthweight is merely a marker for adverse environmental

influences that act in later life.[26] Although this interpretation can just be sustained if one is prepared to view the ecological data in isolation, it cannot account for the results of follow up studies of individuals. In Hertfordshire birthweight was not associated with social class, either at birth or currently. The relations with adult risk factors were present within each social class. Further, 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. But the relations we have found between early growth and adult fibrinogen concentrations and blood pressure are independent of adult height.

A second possible explanation for the relation 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 birthweight are the same as or are closely linked to the genes that determine cardiovascular disease. This explanation is not likely to be correct because birthweight does not seem to be strongly genetically determined[27] nor is there much evidence that cardiovascular disease has, in the vast majority of people, a major genetic component.

We think that the relation between retarded growth in early life and risk of adult disease is due to long term effects 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, though it may explain why the known adult risk factors predict cardiovascular disease in individuals so poorly. Further work is focusing on the nature and timing of environmental factors that influence the growth of the fetus and infant and programme its metabolism. Laboratory studies that allow direct manipulation of the fetal environment in experimental animals are running in parallel with studies in humans that exploit the ability of ultrasound techniques to examine maternal influences on different aspects of fetal development.

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