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Contents

Introduction

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We are assembled to talk about the influence of the childhood environment on adult diseases, and we shall be covering four main areas. The first concerns mechanisms operating in early life which could have a bearing on cardiovascular disease. The second encompasses the interaction of nutrition with the immune system and the long-term effects of infection in childhood. In the third, we shall consider brain growth at critical periods of development and some exciting new ideas about schizophrenia, suggesting that it arises as a consequence of damage to the brain around the time of birth. Finally, we shall move into the area of psychosocial development.

As a group, we are remarkably heterogeneous, necessarily so, and none of us can know much about what will be discussed outside our particular fields. I am happy to admit that my knowledge of pre-alpha cell clustering is quite limited, and when it comes to the species-normative maternal rearing of rhesus monkeys, I am innocent! We must therefore, throughout the symposium, make sure that we all understand the language being used in each area, for the benefit both of our discussion, and of the readers of the book which will be produced.

Where do we expect to get to in this symposium? We cannot, of course, know; but my hope is that we shall become aware that there are a number of areas where the importance of what happens in childhood is much greater than we have previously supposed. We are going to hear, for example, that diet in early life may affect one's lifetime expectation of allergic disease, that schizophrenia and motor neuron disease may originate in infancy, and speculation that the risk of dying from a stroke is essentially determined before birth. As we consider these exciting ideas, I hope we shall attain a sense of how much is known and how much is conjecture.

We will be thinking about mechanisms, and here there are some central concepts. The simplest is that if one really bad event happens in childhood, a major brain injury for example, it has immediate and irreversible consequences. From that we move to instances such as rheumatic heart disease where there is an event in childhood but only after a long interval are its harmful consequences apparent. In poliomyelitis, we have a model of diseases where the timing of the adverse event in childhood is critical in determining its consequences. It may be critical because an organ is at a critical stage of

development, or because the development of an entire function, such as personality or immunological competence, is at a critical stage.

When we discuss blood pressure we will meet the idea that the fetus, threatened by an adverse environment, may raise its blood pressure, which may be an effective response in terms of short-term survival, but may have as its price reduced long-term survival. One suspects there may be psychological analogies of this situation.

Another set of ideas relates to the consequences of infant feeding and social rearing practices. The message that is beginning to emerge is that infant feeding may set up metabolic patterns which determine responses to later challenges from the same stimulus—that is, high fat intake. Similarly, social rearing practices may determine responses to social challenges in adult life.

Professor Michael Rutter, when he talks about psychosocial development, will be introducing another set of mechanisms, a chain of adverse advents—not just the simplest chain, in which some people are especially unlucky and encounter one bad thing after another throughout life, but a more subtle chain in which people experiencing an adverse environment in early life become more likely to put themselves into an adverse environment later on. Even more intriguing is the idea that the interactions of personality with environment early on may lead somebody to *create* their own environment in adult life. There must be a wealth of points to discuss here.

The most easily awaited part of this three-day symposium will be my summing-up at the end. It seems unlikely that I will be able to condense our discussion of wide-ranging ideas into a few succinct sentences. I predict, however, that we shall agree that the environment in very early life is extremely important, and we shall add that this is an area that is seriously under-researched. The question is whether we shall have identified some obvious ways forward for research in particular areas, and whether there are concepts which unify research across the whole field.

We are now about to embark on a journey down many paths. Where will it take us?

The intrauterine environment and adult cardiovascular disease

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Abstract. Two recent findings suggest that maternal nutrition, and fetal and infant growth, have an important effect on the risk of cardiovascular disease in adult life. (1) Among 5225 men who were born in Hertfordshire, England during 1911–1930 and who were breast fed, those who had the lowest weights at birth and at one year had the highest death rates from cardiovascular disease. The differences were large and were reflected in differences in life expectancy. (2) In England and Wales there is a close geographical association between high death rates from cardiovascular disease, and poor maternal physique and health, and poor fetal growth. These findings raise the question of what processes link the intrauterine and early postnatal environment with risk of cardiovascular disease. Blood pressure, a known risk factor for cardiovascular disease, is one link. A recent study of 449 men and women now aged 50 showed that measurements at birth predicted blood pressure more strongly than current measures such as body mass. Levels of clotting factors in the blood and serum cholesterol (two other risk factors) may also be links.

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There is increasing evidence that the intrauterine environment has an important effect on the risk of cardiovascular disease—that is, ischaemic heart disease and stroke—in adult life. This research originated in geographical studies. A puzzling aspect of the epidemiology of ischaemic heart disease and stroke in Britain is that they are more common in poorer areas and in lower income groups. The differences are large, greater than twofold (Gardner et al 1969, Registrar General 1978). For ischaemic heart disease they are also paradoxical, in that its steep rise in Britain and elsewhere has been associated with rising prosperity. Why should rates of ischaemic heart disease be lowest in the most prosperous places, such as London and the home counties? Variations in cigarette smoking and adult diet do not explain these differences.

We have examined the possibility that they result from geographical and social class differences in infant development 60 and more years ago. Past differences in infant development and health in England and Wales were reflected in the

wide range of infant mortality. For example, in 1921–1925 infant mortality ranged from 44 per 1000 births in rural West Sussex to 114 in Burnley in Lancashire. The highest rates were generally in northern counties where large manufacturing towns had grown up around the coal seams. Rates were also high in poor rural areas such as north Wales. They were lowest in counties in the south and east, which have the best agricultural land and are historically the wealthiest (Local Government Board 1910).

We have used infant mortality statistics for England and Wales to compare the present distribution of adult death rates from cardiovascular disease with the past geographical distribution of different causes of infant mortality. These comparisons are made with the country divided into large towns and groupings of small towns and rural areas within counties, totalling 212 areas—a division of the country used in routine statistics since the turn of the century.

Figure 1 shows that the geographical pattern of death rates from cardiovascular disease closely resembles that of neonatal mortality (deaths before one month of age) in the past (Barker & Osmond 1986). At that time most neonatal deaths occurred during the first week after birth and were attributed

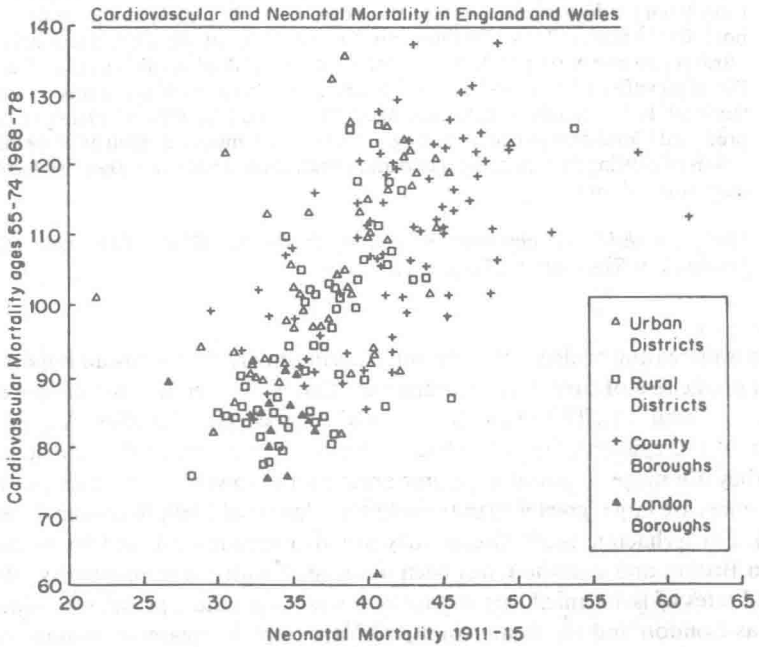

FIG. 1. Standardized mortality ratios for cardiovascular disease (1968–1978) at ages 55–74, both sexes, and neonatal mortality 1911–1915, in the 212 areas of England and Wales.

to low birth weight (Local Government Board 1910). The geographical distribution of maternal mortality, from causes other than puerperal fever, was closely similar to neonatal mortality (Barker & Osmond 1987). Poor physique and health of the mothers was clearly implicated as a cause of high maternal mortality, and was partly a result of the poor nutrition and impaired growth of young girls (Campbell et al 1932). There is therefore a geographical association between high death rates from cardiovascular disease, poor fetal growth and poor maternal physique and health.

In addition to these associations, which indicate the importance of the intrauterine environment, the distribution of ischaemic heart disease is also related to post-neonatal mortality—deaths from one month to one year (Barker et al 1989a). Ischaemic heart disease, but not stroke, is therefore geographically linked to an adverse environment in infancy as well as in fetal life.

Mortality from stroke has fallen in Britain over the past 40 years (General Register Office 1911 et seq). This is consistent with past improvements in the intrauterine environment, as a result of improved maternal nutrition and physique. Ischaemic heart disease mortality, however, has risen steeply. It may therefore have two groups of causes, one acting through the mother and in infancy, and associated with poor living standards, the other acting in later life, and associated with affluence. This later influence seems likely to be linked to the high energy Western diet.

A recent follow-up study gave the first indication that the population associations of cardiovascular disease are also present in individuals. We have traced 5654 men born in Hertfordshire, England during 1911–1930 (Barker et al 1989b). From 1911 onwards, health visitors recorded the birth weights of all babies born in the county and visited their homes periodically throughout infancy. At one year the infant was weighed. The records of these visits have been preserved. Table 1 shows death rates from ischaemic heart disease according

TABLE 1 Standardized mortality ratios for ischaemic heart disease according to weight at one year in 5225 men who were breast fed

Weight at one year (lb)	*Standardized mortality ratios*	
⩽18	112	(33)
19–20	81	(71)
21–22	100	(154)
23–24	69	(85)
25–26	61	(40)
⩾27	38	(9)
All	81	(392)

Numbers of deaths in parentheses. 1 lb = 0.45 kg.
From Barker et al 1989b.

to weight at one year in the 5225 men who were breast fed. Hertfordshire is a prosperous part of England and rates of ischaemic disease are below the national average which, when rates are expressed as standardized mortality ratios (SMRs), is set as 100. Among men whose weights were 18 pounds or less at one year, death rates were around three times greater than in those who attained 27 pounds or more at one year. This is a strong relation: it spans more than 60 years, and it is graded. No similar relation was found in men who were bottle fed from birth, but the numbers were small. Similarly, the numbers of deaths from stroke in this initial sample are too few for analysis. The follow-up is being extended to 20 000 men and women.

Both prenatal and postnatal growth were important in determining weight at one year, since few infants with below average birth weights reached the heaviest weights at one. The lowest SMRs occurred in men who had above-average birth weight or weight at one year (Table 2). The highest SMRs were in men for whom birth weight was average or below and weight at one was below average. Among men for whom both weights were in the lowest group, 5.5 pounds or less and 18 pounds or less, the SMR was 220. The simultaneous effect of birth weight and weight at one year on death rates from ischaemic heart disease are shown in Fig. 2. The lines join points with equal risk of ischaemic heart disease. The values are risks relative to the value of 100 for those with average birth weight and weight at one.

From these findings we conclude that processes linked to growth and acting in prenatal or early postnatal life strongly influence risk of ischaemic heart disease. There is evidence that these processes include (1) the determination of blood pressure in fetal life, (2) long-term 'programming' of lipid metabolism through feeding during infancy, and (3) the early setting of haemostatic mechanisms.

To study the effect of maternal physique and intrauterine growth on adult blood pressure we traced 449 men and women born in a hospital in Preston,

TABLE 2 Standardized mortality ratios for ischaemic heart disease according to birth weight and weight at one year in men who were breast fed

	Weight at birth (lb)			
Weight at one year (lb)	*Below average (≤7)*	*Average 7.5–8.5*	*Above average (≥9)*	*All*
Below average (≤21)	100 (80)	100 (77)	58 (17)	93 (174)
Average (22–23)	86 (34)	87 (67)	80 (29)	85 (130)
Above average (≥24)	53 (14)	65 (42)	59 (32)	60 (88)
All	88 (128)	85 (186)	65 (78)	81 (392)

Numbers of deaths in parentheses.
From Barker et al 1989b.

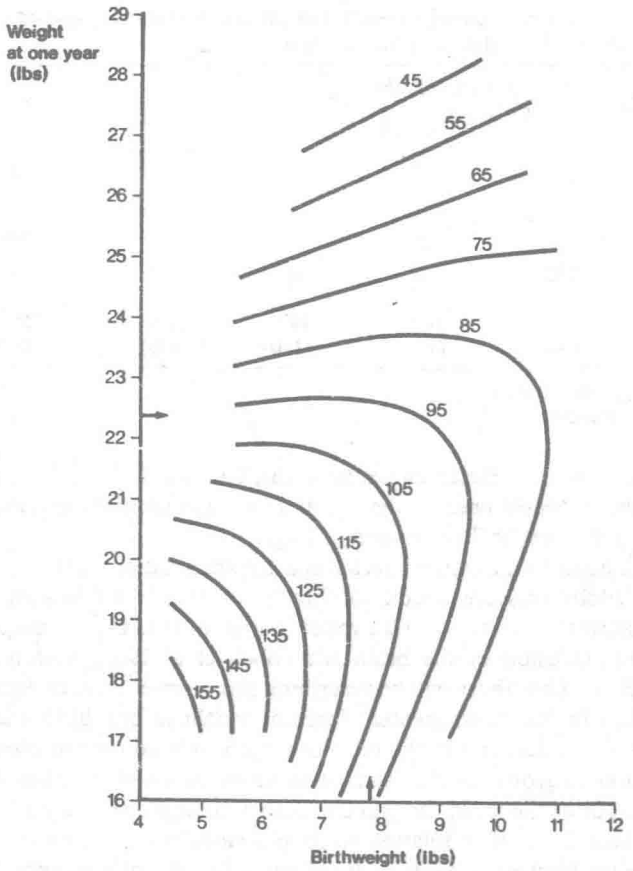

FIG. 2. Relative risk for ischaemic heart disease in men who were breast fed according to birth weight and weight at one year. Lines join points with equal risk. Arrows indicate mean weights. (From Barker et al 1989b by permission of the Editor of *The Lancet*.)

Lancashire during 1935–1943 and measured their blood pressures (Barker et al 1990, Barker 1990). The birth records in the hospital were unusually complete, including, for example, seven measurements of the infant head. We found that the blood pressure and risk of hypertension among men and women aged around 50 years was strongly predicted by a combination of placental and birth weight (Table 3). Systolic and diastolic pressures rose as placental weight increased and fell as birth weight increased. These relations were independent, the highest pressures occurring among people who had been small babies with large placentas. Higher body mass index and alcohol consumption were also associated with higher blood pressure, in keeping with the results of many other studies

TABLE 3 Mean systolic pressure (mmHg) of 449 men and women aged 46 to 54 years according to placental weight and birth weight

Birth weight (lb)	*Placental weight (lb)*				
	−1.0	*−1.25*	*−1.5*	*>1.5*	*All*
−5.5	152	154	153	206	154 (45)
−6.5	147	151	150	166	151 (106)
−7.5	144	148	145	160	149 (169)
>7.5	133	148	147	154	149 (129)
All	147 (68)	149 (171)	147 (120)	157 (90)	150 (449)

Numbers of people in parentheses.
From Barker et al 1990.

(Intersalt Co-operative Research Group 1988), but the relation of placental and birth weight to blood pressure levels, and to established hypertension, was independent of these influences and stronger.

Our data point to a possible mechanism for the relation between placental weight and blood pressure. Studies of fetal blood flow in animals have shown that in response to hypoxia there is a redistribution of fetal cardiac output which favours the perfusion of the brain (Campbell et al 1967, Rudolph 1984). Professor K. L. Thornburg will be describing this phenomenon in detail (1991: this volume). In our data, greater placental weight at any birth weight was associated with a decrease in the ratio of length to head circumference. This disproportionate growth is consistent with diversion of blood away from the trunk in favour of the brain. A fetal circulatory change of this kind, occurring in a fetus that is small in relation to its placenta, could be associated with irreversible consequences, perhaps by changes in arterial structure. There is evidence in animals and humans that changes in blood flow in early life can alter arterial structure and compliance (Berry & Greenwald 1976, Meyer & Lind 1974, Berry et al 1976).

These findings raise the question of what environmental influences act on the mother and determine placental and birth weight. In particular, what determines the discordance between placental and fetal size which leads to high blood pressure? Little is known about this. We suspect that maternal physique and nutrition are the key influences. But at present our conclusion is simply that environmental influences acting in fetal life have a major effect on adult blood pressure and hypertension.

In collaboration with Professor C. N. Hales, of the Department of Biochemistry, University of Cambridge, we are currently examining lipid levels in a sample of men born in Hertfordshire during 1911–1930. Table 4 shows some early results. Among 108 men, all of whom were breast fed, total

TABLE 4 Blood cholesterol and fibrinogen concentrations in men aged 65 years, who were breast fed, according to weight at one year

Weight at one year (lb)	*Cholesterol (nmol/l)*	*Fibrinogen (g/l)*
⩽20	6.9 (16)	3.12 (25)
−22	6.3 (37)	3.07 (47)
−24	6.2 (37)	3.08 (47)
⩾25	6.0 (18)	2.96 (27)

Numbers of men in parentheses.

cholesterol levels were inversely related to weight at one year. This is consistent with the higher risk of ischaemic heart disease in men who were lighter at birth and at one year. As yet, the numbers of men who were bottle fed is too small for analysis. We shall shortly have results for around 500 men. Our tentative conclusion from these early results is that nutrition and growth in fetal and infant life affect adult lipid metabolism. Dr G. E. Mott will be describing experiments which suggest that infant feeding in baboons programmes cholesterol metabolism in the adult (Mott et al 1991: this volume).

Finally, in collaboration with Dr T. W. Meade, we are examining levels of fibrinogen and Factor VII in men in Hertfordshire. Fibrinogen and Factor VII are strongly associated with the risk of ischaemic heart disease (Meade et al 1986, Meade & North 1977). Table 4 shows early results. Among 146 men, fibrinogen levels are inversely related to weight at one year.

In conclusion, detailed geographical analyses in England and Wales suggest that poor maternal physique and nutrition, and poor fetal and infant growth, are associated with increased risk of cardiovascular disease in adult life. In a follow-up study of men born around 70 years ago, who were breast fed, those with the lowest weights at birth and one year had the highest death rates from ischaemic heart disease. Follow-up and examination of men and women who are still alive has shown strong relations between early growth and three major risk factors for cardiovascular disease: high blood pressure, high cholesterol and high fibrinogen. Maternal, fetal and infant influences seem much more important in the causation of cardiovascular disease than we have previously supposed.

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DISCUSSION

Hamosh: Professor Barker, can one dissect out the nutritional effects on later cardiovascular disease in the offspring, both of the mother's nutrition and, even better, the grandmother's nutrition, from the environmental effects of toxins, xenobiotics, and so on? And could one also examine separately the effects of *in utero* maternal malnutrition and/or infant malnutrition (during the first year of life) from later nutrition? For example, if the poorest group, with the poorest