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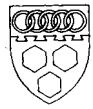

THE CHILDHOOD ENVIRONMENT AND ADULT DISEASE

A Wiley-Interscience Publication

1991

JOHN WILEY & SONS

Chichester · New York · Brisbane · Toronto · Singapore

THE CHILDHOOD ENVIRONMENT AND ADULT DISEASE

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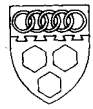
Ciba Foundation Symposium 156



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Contents

Symposium on The Childhood Environment and Adult Disease, held at the Ciba Foundation, London, 15–17 May 1990

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Introduction

D. J. P. Barker

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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

D. J. P. Barker

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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.

1991 The childhood environment and adult disease. Wiley, Chichester (Ciba Foundation Symposium 156) p 3–16

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

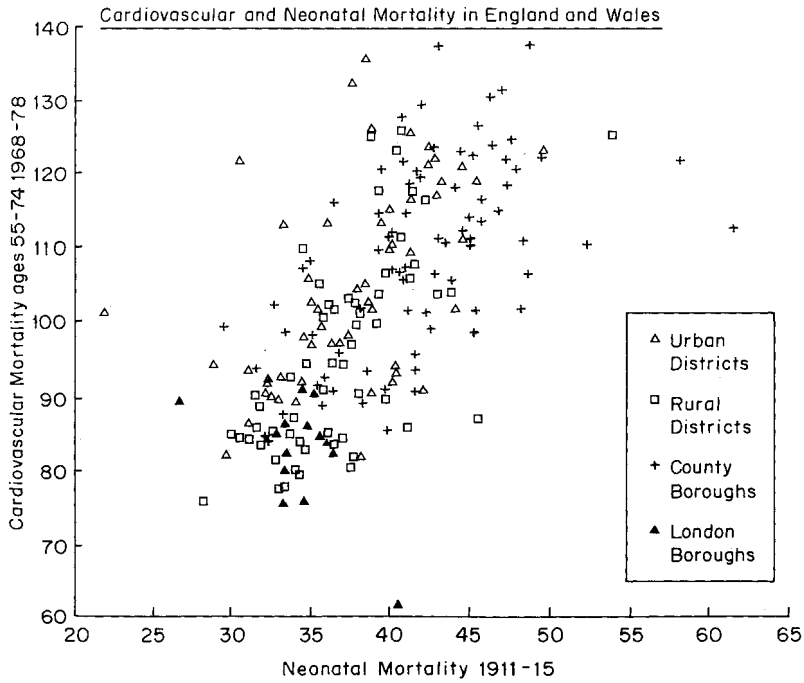

FIG. 1. Standardized mortality ratios for cardiovascular disease (1968–1978) at ages 55–74, both sexes, and neonatal mortality 1911–1915, in the 212 areas of England and Wales.

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.

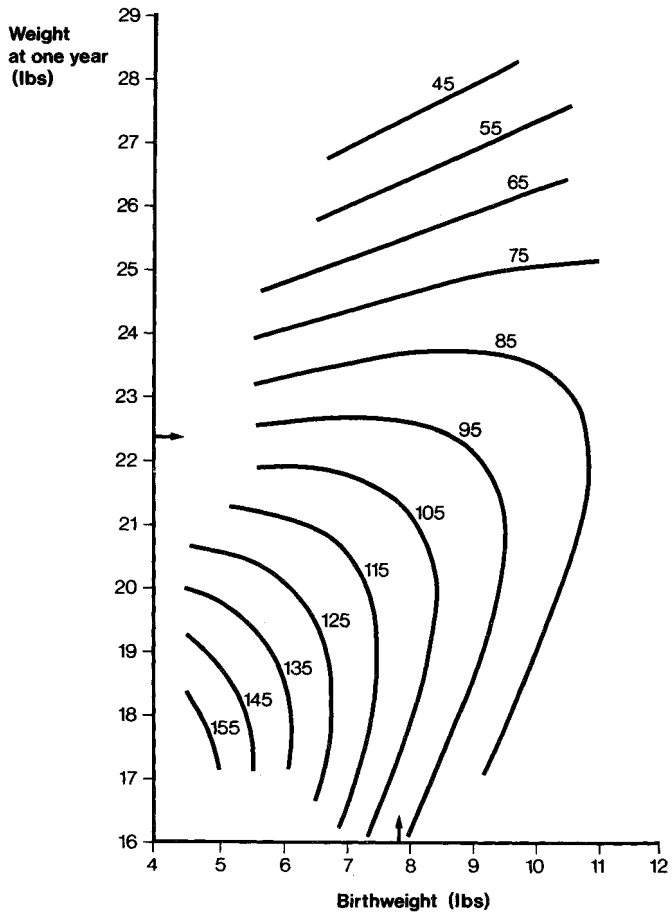

FIG. 2. Relative risk for ischaemic heart disease in men who were breast fed according to birth weight and weight at one year. Lines join points with equal risk. Arrows indicate mean weights. (From Barker et al 1989b by permission of the Editor of *The Lancet*.)

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

predictors, had been transferred after three months or one year of life to the most optimal environment, what would the outcome be in terms of later cardiovascular disease?

Barker: My view is that the evidence does not point to environmental toxins as having important effects on cardiovascular diease. Rather, the evidence points to effects of adverse nutrition of women, going through several generations. Certainly my intention is to focus our research on the nutrition of the mother, and on her physique, which partly depends on her nutrition as a young girl. What we know from a large study of migrants in England and Wales is that people born in areas of low risk of cardiovascular disease—London, for example—carry with them part of their low risk wherever they migrate to within the country. I do not think that the uncertain inferences from migrant studies will tell us the relative importance of early and late nutrition. Rather, understanding seems likely to come from further long-term studies of individuals, and from an understanding of underlying mechanisms.

Hanson: You are arguing that the small, undernourished mother produces a small fetus, and also that she has a relatively large placenta, in relation to fetal weight. You are therefore suggesting that there is some link between maternal nutritional status and placental growth. I would go along with that on the grounds that we don't actually know what controls placental growth. Is this link there in your data?

Barker: It's not there in my data. I suspect that in larger placental size you are seeing a marker of poor maternal nutrition.

Thornburg: It is well known that there is a direct relationship between fetal size and placental size (or placental blood volume) in mammals in general (Owens & Robinson 1988) and particularly in people (Bonds et al 1984). If that relationship is also generally true in the UK, it means that you are basing your relationships on those individuals who don't fit the apparently normal pattern.

Barker: Yes. A lot is known about babies in whom the placenta is relatively small. We are now seeing the other kind of disproportion, where the placenta is too big; and this is new.

Dobbing: The retrospective approach obviously has the usual limitations. Speaking of low birth weight babies in 1921–1922, the low birth weight group is compounded of those born too soon (prematures) and those born too small but of appropriate gestational age. It may be known whether, in 1921–1922, low birth weight babies were more predominantly prematurely born than now?

Barker: More of them were premature than now, but my understanding of the literature at that time is that most small babies were the result of intrauterine growth retardation, not prematurity.

Dobbing: Whichever way it was, it would make a difference to one's further thinking about mechanisms for the phenomena you are suggesting. Also, if the low birth weight babies were predominantly small-for-dates babies, it would again be important to know what variety of small-for-dates they were, because

only a proportion of them are thought to be due to what might loosely be called 'fetal malnutrition'.

Barker: Yes. In the Preston study, the length of gestation of most of the subjects was known. It was unrelated to subsequent blood pressure. There is therefore no evidence that premature expulsion from the uterus is a risk factor for high blood pressure. Secondly, the characteristic of the babies whose placental weight is too great in relation to their birth weight is that their head size was big in relation to their length.

Dobbing: So they were disproportional small-for-dates babies? If so, I think that is an important aspect which should be stated, quoting the supporting evidence. Again, I wonder whether the range of variation in placental weight might be partly due to blood content and, if that is so, whether something about the physiology of the expulsion of blood from the placenta before it was weighed might have a bearing on this mechanism.

Hanson: You are suggesting that the weight of the placenta may be affected by whether or not the blood has been squeezed out before the placenta is weighed?

Dobbing: Yes, either squeezed by the midwife, or squeezed by the placental vessels themselves, which would be more interesting. It is conceivable that the vascular properties of some placentas squeeze the blood out more, and others less so, which would account for that difference in weight—a difference that is not great in relation to the blood content of the average placenta.

Hanson: Certainly the fascinating point about David Barker's findings is that one is not dealing with very large placentas or with very small babies; both are within the normal range.

Lloyd: Do you really have those data? You simply specified babies 'under 5.5 lb'; do you know how many were very much smaller?

Barker: The smallest baby was 3 lb 2 oz and the next two were 4 lb.

Lloyd: I am interested in the maternal weights, because you talked about maternal undernutrition. Do you actually have any data on maternal nutrition, or is it just supposition that these were undernourished mothers?

Barker: The only data in Preston are on maternal pelvic size, which correlated strongly with birth weight, as one would expect. In another set of data in Sheffield which we discovered subsequently, and are now doing the same study on, we do have maternal weights.

Chandra: One situation where the birth weight is low and placental weight relatively high is intrauterine infection. Such infections are more common in women from the lower socio-economic levels or in those who are undernourished.

Casaer: Was the distribution of the placental weights by any chance bimodal?

Barker: We don't see this. The distribution of placental weight approximates to a normal distribution skewed to the right. It's not bimodal.

Chandra: Are the subjects you have analysed in Hertfordshire those who had *not* migrated out of the area?

Barker: Out of 7991 boys born in the study period, 5654 were either living in England and Wales, or had died.

Chandra: Another question relates to the recording of birth weight, or weight at one year. Those of us working in these areas feel that it needs a lot of training of the individuals who weigh infants, and very accurate scales, to achieve the minimum possible intra-observer or inter-observer variance. Since these infants in rural Hertfordshire in the 1911–1930 period were weighed on potato scales, and when one weighs potatoes one often rounds them up the nearest half pound or pound, would that have made any big difference to the overall assessment?

Barker: The crudeness of the measurements is in stark contrast to the precision of the predictions. Presumably, these predictions would have been better still if the weights had been measured better!

Richards: Taking up the issue of migration, height is correlated with social class, and assortative mating (the tendency of people to marry people with similar characteristics to themselves) is strong for height. Social mobility is also related to height, for both men and women, with taller individuals more likely to be upwardly mobile. This ought to mean that, if height is a rough indicator of maternal physique, there may be a selective effect whereby populations in the poorer rural and industrial areas will lose, through migration, their fitter and taller members. Women moving out of such areas may tend to be those who are taller and are likely to produce bigger babies. This may exaggerate the effect that you show in your geographical distributions. This may be relevant to the question of London, where historically there has been a strong inward migration of, presumably, the healthier women coming from the poorer areas, as well as the healthy men.

Barker: That is an extremely helpful comment, which fits in with what we know occurred, from Charles Booth's survey (*Life and Labour in London*), namely that there was a constant renewal of London by immigration of the fittest young women from an area which started in the west, in Devon, and extended up to Norfolk. They mostly came for one reason, domestic service, in which employment they continued to be well nourished. The picture was of London sucking in generations of the best young women, who had the lowest mortality in childbirth, and whose babies had the lowest neonatal mortality. Thereafter, their children had a poor environment and, as Booth wrote, 'after two generations London life reduces the immigrants' descendants to the level of those among whom they live'.

Hamosh: Do you have data on the siblings in your Hertfordshire study? I ask this because I would like to know how long the breast-feeding period was at that time. Could it be that maternal reserves were depleted by the time a second baby was conceived and born?

Barker: I have that information, because we have data on all the children born in Hertfordshire over a 35-year period. We have not yet looked at the effect of parity.

Lucas: The increase in vascular diseases is very recent and has occurred in only some Western countries, but presumably adverse perinatal and childhood factors, maternal malnutrition, variations in placental weight, and the other factors you talked about, would have existed in previous centuries and in other cultures where the incidence of vascular disease was very low. How do you fit that into your scheme?

Barker: The ecological data suggest that stroke mortality is related principally to events in intrauterine life. The suggestion that is emerging is that blood pressure is 'set' during the intrauterine period. Stroke mortality has declined every year for the past 40 years in Britain and in many other countries, which is consistent with past improvements in maternal physique and health. By contrast, ischaemic heart disease mortality has risen very steeply in industrialized countries, so there is something else, perhaps involving cholesterol metabolism or clotting factors, that is set in early life. To explain the distribution of ischaemic heart disease it is necessary to postulate two sets of factors: one related to poor living standards, which operates in very early life, and another set relating to good living standards which operates later, and presumably is associated with the high energy Western diet.

Mott: Your follow-up of individuals still living, in the Hertfordshire study, is extremely important. Measuring lipoprotein cholesterol would be valuable in addition to total serum cholesterol, because, at least in the non-human primate, programming effects of early diet act primarily upon the lipoproteins and not on the total serum cholesterol.

Barker: We are indeed measuring lipoprotein in people born in Hertfordshire.

Wood: Rather naively, but hopefully, I am wondering whether our present feeding practices for newborns are also going to reduce the problem of cerebrovascular and ischaemic heart disease further in 30 years' time. In the UK we now have better-fed babies, who are fed on demand. We still have low birth weight babies, but we have very much lower neonatal mortality than in the period you are discussing. In addition, we have another small cohort of very small preterm babies who are preserved in the face of immense difficulty. One would like to think that our improved neonatal practices are likely to influence outcome in terms of blood pressure and cardiovascular disease; but if the setting of, say, peripheral resistance is predetermined, before the fetus gets near to the time of delivery, such expectations and aspirations may be over-optimistic.

Barker: The framework of ideas within which we are working is that circulatory adaptations in the fetus lead to changes in arterial structure, with reduced compliance. This in turn leads to higher pulse pressure, and to further charges in arterial structure. This feedback could perpetuate high levels of systolic pressure from infancy to old age.

Thornburg: In your Fig. 1 (p 4) you plotted cardiovascular mortality at ages 55 to 74 as a function of infant mortality. I was interested in the outliers. There were occasional points where the infant mortality seemed to be rather high, yet the death from cardiovascular disease was rather low. Can you learn anything about the outliers? Do they fit in with your hypothesis on nutrition, for example?

Barker: Unfortunately, the outliers are simply places that are extremely small, such as the City of London, which was a London borough with few inhabitants. Mortality rates in these places are liable to wider fluctuations.

Thornburg: So the answer is that you can't learn from these points? Can you learn anything from the Dutch study of the Hunger Winter of 1944 to 1945 (Stein & Susser 1975), when many people in Holland starved?

Barker: Yes. The offspring, who were *in utero* at that time, have been followed up. People who were *in utero* in the last trimester of pregnancy during that winter, although born small, were of normal height and had normal intellectual development at age 18. More recently, Dr Lumey has studied those who were *in utero* in the first trimester at that time; they were born with normal weight and at 18 had normal height, but when the women had babies, their babies were smaller than predicted (Lumey 1988).

Suomi: In the United States today there is a relatively large cohort of babies being born to extremely small mothers, and they are typically born unusually small. This is not so much because of the other factors mentioned, such as prenatal diet, but because the mothers are very young, 13–15 years of age. Do you have any thoughts on the degree to which your findings might generalize to this population?

Barker: In the UK, women having children young was a feature of coal-mining communities, who have conspicuously bad health. However, there were few very young mothers in the Preston study and we do not know mothers' ages in Hertford. So I cannot generalize here.

Dobbing: You didn't tell us whether it was better to be breast fed or artificially fed, in the Hertfordshire study. I suppose it can be assumed that qualitatively the breast milk in those days, in the earlier part of this century, was not much different qualitatively from nowadays, although quantitatively it may have been; whereas the artificial food is likely to have been very different from now. Apart from that, is it better to have been breast fed in 1922?

Barker: Although, on the face of it, it was better to have been breast fed in Hertfordshire, in terms of the overall lower mortality rates from ischaemic heart disease, we don't yet have sufficient numbers to take account of the fact that the babies who were bottle fed were different; they were, on average, smaller at birth, and one needs to allow for that. In the Hertfordshire study, the information that I long to be able to give Glen Mott is whether the cholesterol levels are higher in the breast-fed or the bottle-fed people, taking account of birth and infant weight.

Dobbing: Yet the breast-fed individuals would have had higher cholesterol levels in infancy.

Hamosh: But that could be a transient phenomenon, during the day, with breast feeding.

Dobbing: We are talking of transient phenomena.

Richards: This very small minority of mothers who chose to bottle feed in the 1920s would be nothing like a bottle-feeding group today. Choice of feeding method has varied greatly over time, so the social composition of a group choosing a feeding method will be specific to a particular historical period. In so far as social factors are related to maternal health, there may also be differences in the growth and health of babies produced by mothers who opt for each feeding method.

Barker: There's every reason to believe that that is true. We know quite a lot about the kind of artificial infant feeding preparations available in 1920. They were extremely varied in their compositon. They were widely used in Lancashire cotton towns, where women returned to work soon after delivery, leaving their babies in the care of child minders. In places like Hertfordshire, artificial feeds were not widely used. It was a community with a tradition of breast feeding, and with a 200-year history of being a wet-nursing area for babies brought out from London. There wasn't much cows' milk available because it was mostly sold to London. So the minority of mothers who did not breast feed must have been unusual. What they fed their babies with, we cannot tell.

Casaer: Were they not the infants whose mothers died?

Barker: No. It wasn't that; we know that much.

Murray: There were striking seasonal variations in infant mortality at the time of the First World War, and earlier. Have you looked at the effect of season of birth in your study?

Barker: There were seasonal variations in post-neonatal mortality (that is, deaths from one month to one year). These variations were due to higher rates for respiratory mortality in the winter and for diarrhoeal disease in the summer, but the relationships that we are looking at are primarily with *neonatal* mortality.

Murray: Still births also showed a variation, but not to such an extent.

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