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# Is the child father of the man?

## *Controversy about the early origins of cardiovascular disease*

When are the seeds of ischaemic heart disease sown? Traditionally factors related to lifestyle—such as diet, exercise, and smoking—have been blamed. These are regarded as operating mainly in adult life—hence the focus of attempts at intervention. Challenging this view are Professor David Barker and his colleagues in the Medical Research Council Environmental Epidemiology Unit at the University of Southampton.[1-13] They have shifted the focus of attention to factors in fetal life and infancy and argued that they may profoundly affect the subsequent risk of cardiovascular disease.

Their "programming hypothesis" started from the paradox that, although the lifestyle hypothesis predicts that increasing affluence should increase the risk of cardiovascular diseases, in England the diseases are commoner among poorer people. The group took up the observation that places currently with high mortality from ischaemic heart disease and stroke used to have high infant mortality. Could factors that adversely affected infant health also cause disease in later life?

Their studies of mortality suggested possible relations between early influences and later diseases.[1-3 5] To find out which structural and functional changes in early life led to later proneness to disease the group moved to studies of individual people. In an ingeniously devised series of longitudinal studies, using data more than 50 years old on the gestation and infancy of the subjects, the group showed that fetal growth, and growth and nutrition in infancy, importantly affected risk factors for cardiovascular disease in later life. These included plasma concentrations of cholesterol, apolipoprotein B,[12] and fibrinogen[10]; blood pressure[11]; body fat distribution[13]; and liability to impaired glucose tolerance and diabetes.[11]

The Barker group suggested an addition to the programming hypothesis to explain one aspect of the geographical paradox that prompted their research.[2 14] Although ischaemic heart disease, chronic bronchitis, and stroke are all more common where infant mortality was previously high, the secular trends in these diseases differ. Chronic bronchitis and stroke have become less common as ischaemic heart disease has become more common: factors in addition to those determining infant mortality rates must therefore contribute to the cause of ischaemic heart disease. The group suggest a combination of factors associated with early adversity followed by factors associated with later affluence. They have presented evidence for such a two phase mechanism in the aetiology of non-insulin dependent diabetes.[11]

Predictably, such threats to the prevailing orthodoxy have not gone unchallenged. Two reviews, both highly critical of the programming hypothesis, have recently been published.[15 16] The first considered 10 "ecological studies" (five of them by the Barker group), which examined geographical differences in cardiovascular mortality or risk factors in relation to infant mortality or other indicators of early life experience. The review's most important criticism was that the effects of continuing social disadvantage had not been adequately taken into account: the high adult mortality from cardiovascular disease in areas with previously high infant mortality rates may have resulted from continuing adverse factors. In addition, the specificity of the relation was questioned—infant mortality correlates with mortality from many adult diseases, not just those selected by the Barker group for attention.

Only one of the ecological studies apparently contradicted the Barker group's hypotheses.[17] It showed that when measures of contemporary deprivation or affluence were taken into account the relations between earlier infant mortality and later adult disease were greatly reduced, although they did not totally disappear.

A second critical review considered 12 longitudinal and four case-control studies relevant to the hypothesis.[16] They were variously criticised on the grounds that persisting disadvantage had not been taken into account or that the findings were inconsistent internally or with those of other studies. The results of only two papers, however, directly conflicted with those of the Barker group—the British regional heart study of the effects of migration suggested, contrary to the Barker group's finding,[5] that where men live is more important than where they were born in determining blood pressure[18] and mortality from ischaemic heart disease.[19] And a study from Israel[20] failed to show, at age 17, the relation between birth weight and later blood pressure found in several population groups at different ages by the Barker group.[8 9 21]

The first critical review concludes that "hypotheses generated by ecological studies need to be rigorously tested in epidemiological studies based on individuals rather than groups," and the second that "there is still insufficient evidence to claim that experiences early in life determine the subsequent risk of cardiovascular disease."

These criticisms deserve further comment. Firstly, the group's work has been advancing rapidly—its studies have moved from the ecological ones, which can only generate

hypotheses, to studies on individual people, which have provided evidence for the programming hypothesis in relation to several important physiological and biochemical variables.

Secondly, there are features in the Barker group's results that argue against the most important criticism (the failure to recognise continuing adverse circumstances as a confounding factor). Barker's group have established that relations between early experience and later disease or physiological change are very specific in their times of operation. Even in the geographical studies it is not a question of all indicators of early disadvantage correlating with all the diseases of interest. Stroke is linked to earlier maternal and neonatal mortality, chronic bronchitis to postneonatal mortality, and ischaemic heart disease to both neonatal and postneonatal mortality.

If the early mortality indices were simply acting as markers of later adversity we would not expect these specific relations. Similarly, the studies on individual people show very specific relations between growth at a particular phase—for example, in fetal life or infancy—and later measurements of blood pressure, glucose tolerance, and concentrations of cholesterol and fibrinogen.

Though studies of mortality could not control for the effects of continuing socioeconomic factors because the information was not available, in the studies of living people the relations found between early weight and later risk factors were independent of socioeconomic status, either currently or at birth.[8 9 21]

What should the uncommitted reader make of this controversy? The topic is too important to be regarded simply as an intriguing debate between two schools of epidemiology. One view would be that the Barker group are misled, either in their findings or, as Elford *et al* suggest, in their interpretation. This is difficult to accept, given the coherence and logic of the Barker group's studies, which have used several populations and sought several different types of data to test their hypothesis. Another view is that both groups are right, that both very early influences and later ones contribute to the causes of ischaemic heart disease and that the dispute is really about the relative importance of each.

Such a compromise view, however, would not explain the geographical paradox, which began the Barker group on their inquiries. Nor do Elford and colleagues offer an alternative explanation of this in their criticisms of the programming hypothesis.

A third possibility is that we are witnessing the beginning of one of Thomas Kuhn's "paradigm shifts."[22] The lifestyle paradigm for the aetiology of ischaemic heart disease seems to be unable to account for the geographical epidemiology of the disease—at least in Britain. The "early life experience" paradigm is a strong candidate for its replacement.

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# The supraregional assay service

## *About to lose the benefits of centralisation*

Few doctors have much to do with the supraregional assay service: a busy general hospital with an active clinical endocrinology department might send it requests for one adrenocorticotrophic hormone, two parathyroid hormone, and eight growth hormone assays a month. Yet the service has been a success since it was set up in 1974—a model of rationalisation. In some ways it could be taken as a microcosm of the wider NHS of which it is a part, in which case what's happening to it now as a result of the government's reforms may provide a pointer to what to expect in other parts of the NHS.

The service was set up in response to the uneven distribution of facilities provding specialised laboratory investigations.[1-3] More than 20 centres now provide technically complex or infrequently requested assays of hormones, proteins, tumour markers, drugs, trace metals, and enzymes in genetic tissue.

Centralisation brought its advantages. It minimised the problems of maintaining the quality of assays done in small numbers or infrequently. (Paradoxically, results were usually available more quickly if the assays had been done locally.) The service provided hospitals with expert advice on the interpretation of results. The centres developed new assays—for example, of gastrointestinal hormones, androstenedione, and insulin C peptide. Assays previously available only from the service were improved, meaning that assays for thyroid hormones, thyroid stimulating hormone, gonadotrophins, and prolactin could be devolved to general hospitals—whose laboratory staff were offered training at supraregional centres. Because clinical chemists in referring to hospitals were responsible for ensuring that requests were appropriate, the service was less abused by inappropriate requests than many other investigative services.

Although initial funding came from the Department of Health and Social Security,[4] local health authorities were