Early programming of adult diseases in resource poor countries

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Arch Dis Child 2005;90:429-432. doi: 10.1136/adc.2004.059030

Considerable evidence now exists to suggest that early exposure to nutritional deprivation can have long term consequences to health, with low birth weight now considered a risk factor for later health outcomes such as coronary heart disease, stroke, type 2 diabetes, and the metabolic syndrome. Of importance, such effects are most exaggerated when faced with over-nutrition in later life, forming the basis for the "thrifty phenotype" hypothesis. The evidence in support of these associations comes largely from retrospective cohort studies in which adult outcomes were correlated with birth weight records. Relatively little data is available from developing countries, where long term record keeping of birth weight data has not been a high priority. Arguably however, such countries are at the greatest risk from the mismatch of early nutritional deprivation and later nutritional affluence. This paper explores the importance of the "developmental origins of health and disease" hypothesis in resource poor countries.

particularly vulnerable to nutritional insults, and that certain organs such as the brain tend to be spared at the expense of others.³

At the current time Barker's theories still remain the subject of intense scrutiny and not inconsiderable controversy,⁴ but few would now deny the underlying tenet that early exposure to nutritional deprivation can have long term consequences to health. In summary, there is considerable evidence that fetal and early post-natal undernutrition can invoke the following changes: *metabolic adaptations* that affect variables such as hepatic enzyme profiles,⁵ lipoprotein profiles,⁶ and clotting factor production;⁷ *anatomical adaptations* that affect processes such as end organ glucose uptake⁸ and renal solute handling;⁹ and *endocrine adaptations* that affect the hypothalamic-pituitary-adrenal axis,¹⁰ insulin signalling,¹¹ and leptin levels.¹² These changes map onto health outcomes such as coronary heart disease, stroke, type 2 diabetes, and the metabolic syndrome, all of which have been shown to be increased in low birth weight babies.³

The evidence for these associations originated largely from retrospective cohort studies in which adult outcomes were correlated with birth weight records. The main controversies over the evidence have centred on four questions: (1) whether socioeconomic differences (which can affect both birth weight and later health) have been adequately controlled for in the analyses; (2) the possibility that the correlations between low birth weight and later outcomes could arise from a common genetic factor that affected both;¹³ (3) statistical issues in relation to how we adjust for later changes in body size and fatness;¹⁴ and (4) failure to replicate the observations in all studies. Reinforcement for the cross-sectional analyses has come from a wide range of mechanistic studies in animal models in which the effects of maternal nutrient restriction during pregnancy and lactation can be investigated more easily at the biochemical level.¹⁵ Finally there have been studies showing that babies randomised to different forms of feeding in early life show profound later sequelae, even when the period of randomisation was extremely short.¹⁶ Thus, although there remains much to be learnt, the totality of evidence is strong and it is

In the late 1980s Prof David Barker and his colleagues from Southampton observed that the geographical distribution of heart disease in the UK was more closely related to a person's place of birth than where they currently lived.¹ This suggested that early life events can cause permanent changes in physiology that, depending on the environment, may later predispose people to disease. Associations with birth weight and with growth in infancy suggested that early nutrition was an important component of these "programmed" effects. These first clues opened up a vast new area of research in a field now officially termed "the developmental origins of health and disease" (DOHAD).

In fact suggestions that early life events can impose permanent changes to human form and behaviour stretch back several millennia to the earliest debates about "nature versus nurture". We can trace these thoughts through the ideas of people such as Lamarck in relation to "organic evolution",* and Pasteur in terms of early modification of the immune system. In this century the main proponents of early programming were Robert McCance and Elsie Widdowson,² whose experiments on caloric restriction of piglets and rats established several of the underlying principles of modern day "Barkerology"; namely that there are critical windows in which a growing organism may be

*It is particularly interesting that Lamarck's ideas that physical changes adopted in one generation could be transmitted through the gamete to the next generation are now being validated by discoveries in relation to transgenerational effects on outcomes such as birth weight and epigenetic imprinting.

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A focus on thrifty genotypes and thrifty phenotypes

The latter half of the last century saw virtual epidemics of type 2 diabetes in many traditional populations, as their lifestyles changed from hunting, gathering, and subsistence agriculture to a modernised pattern characterised by sedentary occupations and energy-dense foods.³⁹ These changes were highlighted in a number of specific population groups, such as the Micronesian populations of the small Pacific island of Nauru³⁹ and the Pima Indians of Arizona.⁴⁰ In 1962, as a preliminary explanation for this observation, JV Neel proposed the “thrifty genotype” hypothesis.²⁰ To Neel, type 2 diabetes presented an enigma in that a relatively frequent disease, which often interfered with reproduction by virtue of its onset during the reproductive or even pre-reproductive years, had continued to exist and even to increase in prevalence. To have persisted through centuries of evolution, and in the face of the obvious and strong genetic selection against this condition, the diabetogenic gene or genes must have had some survival advantage. Neel’s “thrifty genotype” hypothesis suggested therefore that the diabetogenic gene, or genes, persisted at a high level in the population because they somehow conferred a survival advantage in times of nutritional deprivation, though were detrimental at times of adequate or over-nutrition.

With the emergence of preliminary evidence to suggest a relation between indices of fetal and infant growth and adult disease in the early 1990s, Hales and Barker suggested the “thrifty phenotype” hypothesis in the aetiology of type 2 diabetes.⁴¹ The concept underlying their hypothesis is that poor fetal and early postnatal nutrition imposes mechanisms of nutritional thrift on the growing individual, and that this results in impaired growth of cells and organs, and hence programming fetal metabolism for nutritional adversity. This physiological state is appropriate as long as the individual persists in the undernourished state. When faced with good or over nutrition in later life however, the physiology is overwhelmed, and disease occurs. The hypothesis was later expanded to include the proposal that the emergence of pathological changes following undernutrition in early life was also critically dependent on the superimposition of other factors, notably obesity, ageing, and physical inactivity.⁴²

Whether the recent epidemic of chronic disease in resource poor countries is a consequence of thrifty genes, or of a thrifty phenotype, public health practitioners now face the difficult task of attempting to direct limited resources both at improving poor maternal and infant nutrition, while at the same time attempting to curb adult over consumption and the emerging epidemics of obesity and chronic disease.

therefore not surprising that the topic has been one of the dominant themes of nutritional research in the past decade.

SIGNIFICANCE OF THE THEORY IN LOW INCOME AND TRANSITIONAL COUNTRIES

An important element of the early programming thesis is that the underlying metabolic defects entrained in early life seem to translate into later disease only when the organism becomes overweight or obese; in other words when the early adaptations that have been invoked to survive under restricted nutrient supply (the so called “thrifty phenotype”¹⁷) are inappropriate to the later conditions of affluence and plenty.^{18–19} In an analogous way it has been argued that evolutionary pressures from famine and starvation have created a “thrifty genotype” that is advantageous when times are hard but is “rendered detrimental by progress”.²⁰

Current thinking is that a combination of a thrifty genotype and a thrifty phenotype amplifies the predisposition of populations in developing countries to developing diseases of affluence. This is particularly so in countries passing through a rapid economic and nutritional transition, or in peoples from poor countries who migrate to wealthy ones.²¹ The evidence in support of this is pieced together from a variety of different observations involving, for instance, the increased susceptibility of peoples of Asian origin to diabetes²² and of African origin to hypertension.²³ In such work it has proved difficult to separate out in-born genetic effects from life-time programmed effects, but both are considered significant.

With regard to the early-life programming hypothesis it must be admitted that there is a scarcity of data from developing countries because almost no institutions in such countries have maintained reliable archives of birth records which can be compared against adult health outcomes. Nonetheless the theory is that when there is a transition from energy and nutrient deprivation in early life to abundance or over-abundance in later life this generates a disadvantaged state that is especially prone to metabolic disease (fig 1).

Studies from Mysore in India have shown evidence that later outcomes are associated with birth weight and length,^{24–25} but the data do not permit the conclusion that these associations are any stronger than seen in European or American cohorts. A small number of other studies from developing countries similarly support the early programming theory, but without any evidence of any additional potency. Importantly a study from The Gambia²⁶ failed to find any association between early life growth faltering and later metabolic disease, but concluded that this was because the adults being studied were still living in harsh environment in which they remained lean, physically fit, and on a frugal diet—thus remaining within the “adapted cycle” illustrated on the left hand side of fig 1.

The most persuasive evidence that the thrifty phenotype phenomenon may be associated with a greatly increased risk of metabolic disease in populations in transition comes from the work of Ranjan Yajnik and colleagues in Pune, India. Stimulated by the work of David Barker and Caroline Fall from Southampton, the Pune team have studied the early genesis of insulin resistance in Indian babies. They have used anthropometric measurements of babies to describe their morphology at birth. The picture that emerges is of Indian babies that are much smaller than those in Southampton in all respects except measures of body fat; especially central fat as judged by the subscapular skinfold thickness.^{27–28} They describe this as the “thin-fat” baby syndrome and believe that it shows that the excess visceral adiposity of most Asian adults can be traced back to the neonate. In the babies of urban mothers in Pune, cord blood insulin levels appear raised when compared to the Southampton babies, and are correlated with subscapular skinfold thickness.²⁷ Later in childhood these thin-fat Indian babies can be shown to have profoundly impaired indices of insulin sensitivity which are inversely correlated with birth weight.^{29–30} Yajnik’s studies provide the first real data to substantiate the claim that people in developing countries will suffer the greatest effects of early programming.¹⁸

EVIDENCE THAT IMMUNE FUNCTION MAY ALSO BE PROGRAMMED

In 1997 we published data from The Gambia showing that young adults who had been born in the annual hungry season were significantly more likely to die from infectious diseases^{31–32} (fig 2). This suggested that fetal undernutrition (or possibly an infectious or toxic insult correlated with season of birth) could cause a permanent impairment of the

Figure 1 Schematic representation of the transitionally disadapted state affecting mothers and babies as populations make a rapid transition from nutritional poverty to affluence.

immune system, and we have subsequently been exploring the possible biological mechanisms. To date our follow up studies show that the hungry season is associated with a smaller thymic size,³³ altered patterns of T cell subsets with a lower CD4/CD8 ratio,³⁴ lower concentrations of T cell receptor excision circles (TRECS) suggestive of a lower thymic output,³⁵ and lower levels of maternal breast milk IL7 which is a putative thymic trophic factor.³⁵ Additional studies by

ourselves and others have shown that antibody responses to vaccination with a polysaccharide antigen (typhoid Vi vaccine) are significantly positively related to birth weight.^{36, 37}

These findings provide early clues to support the concept of a programming of immune function, but much remains to be done to refine the details. Nonetheless the likelihood that early-life nutrition can have a profound and lasting effect on immunity could have important consequences for outcomes such as autoimmune diseases and cancer surveillance, in addition to the more obvious role in susceptibility to infectious diseases.

CONCLUSIONS

It is a reasonable inference that the fetal origins theory is of greatest relevance to the developing world, and, if true, the implications for global health are enormous. Around 95% of the world's growth retarded babies are born in developing countries, and a recent WHO/FAO report on "Diet, Nutrition and the Prevention of Chronic Diseases"³⁸ predicted that a global epidemic of obesity driven type 2 diabetes will soon dominate chronic disease healthcare. At the same time such countries still suffer the "double burden" of the unfinished agenda of infectious diseases and the emerging agenda of non-communicable diseases. It seems inevitable that the transition from the adapted cycle on the left hand side of fig 1 to the readapted cycle on the right hand side must pass through the disadapted phase. How best to ameliorate the

Figure 2 Kaplan-Meier survival plots by season of birth.

health effects of this transition should be one of the leading challenges facing obstetricians and paediatricians working in low income countries.

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Competing interests: none declared

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