Saturday 17 February 2001

BMJ

The fetal origins of adult disease

No longer just a hypothesis and may be critically important in south Asia

David Barker pioneered the idea that the 20th century epidemic of coronary heart disease in Western countries might have originated in fetal life.[1] Paradoxically, the epidemic coincided with improved standards of living and nutrition, yet in Britain its greatest impact was in the most deprived areas. Barker observed that early in the 20th century these areas had the highest rates of neonatal mortality and by inference the highest rates of low birth weight. He postulated that impaired fetal growth might have predisposed the survivors to heart disease in later life. The first world congress on the fetal origins of adult disease in Mumbai earlier this month provided an opportunity to assess the state of the hypothesis and consider its implications for future research and policy.

Barker's group originally examined cardiovascular mortality in men born in Hertfordshire, England, in the early decades of the century, on whom good records had been kept of size at birth and growth in infancy. Deaths from ischaemic heart disease were indeed commoner in men who had been small at birth and at 1 year. This kind of retrospective cohort study depends on anthropometric measurements in infancy having been preserved. At least seven such studies have shown that lower birth weight is associated with higher risks of later ischaemic heart disease and diabetes or impaired glucose tolerance. These and many other studies have shown that lower birth weight is associated with higher blood pressure in childhood and adult life (C Martyn*). However this effect is relatively small—2-3 mm Hg higher blood pressure for 1000 g less of birth weight. Neither the higher blood pressure nor other recognised risk factors account for the association of low birth weight with heart disease.

The evidence for the association of adverse adult outcomes with lower birth weight is strongest for blood pressure and impaired glucose tolerance (D Leon). Those outcomes can be measured earlier in life, and more data are available, including some prospective studies. Though fewer studies link heart disease to low birth weight, and some are confined to men, the evidence looks convincing. Barker's original hypothesis is confirmed. The few studies on stroke suggest the same association, particularly for haemorrhagic stroke (D Leon, J Rich-Edwards).

The effects of impaired fetal growth are modified by subsequent growth: the highest risks of heart disease and of type 2 diabetes, the insulin resistance syndrome, or impaired glucose tolerance (collectively referred to below as impaired glucose tolerance) are in those who were small at birth but became overweight adults. This led to the second part of the hypothesis proposed by Barker and Hales: the idea of the "thrifty phenotype."[2] As an adaptation to undernutrition in fetal life permanent metabolic and endocrine changes occur which would be beneficial if nutrition remained scarce after birth. If nutrition becomes plentiful, however, these changes predispose to obesity and impaired glucose tolerance.

The congress heard a wide range of research that these hypotheses have stimulated. The patterns of prenatal and postnatal growth that predispose to the two major disease outcomes—ischaemic heart disease and impaired glucose tolerance—are complex (D J P Barker; J Eriksson and C Osmond). In general the most unfavourable growth pattern is smallness and thinness at birth, continued slow growth in early childhood, then acceleration of growth so that height and weight approach the population means. A continuing rise in body mass index above the mean is associated with impaired glucose tolerance. However, the patterns differ by sex and also by ponderal index (a rough measure of fatness) at birth. Whether or not the thrifty phenotype is the mechanism, low birth weight and high body mass index undoubtedly interact: their effects on blood pressure and impaired glucose tolerance are multiplicative (D Leon). Birth weight and ponderal index (as well as body mass index) are crude measures of how fetal nutrition has affected body composition and of the balance between lean body mass and fat, so the true size of the effect of fetal growth on later disease is hard to measure.

The hypothesis predicts that more heart disease and impaired glucose tolerance will be seen in a population that is undergoing transition from sparse to better nutrition. Holding the conference in Mumbai was therefore appropriate: the incidences of type 2 diabetes and ischaemic heart disease are rising rapidly in India, coinciding with increasing urbanisation and obesity. Indian babies are exceptionally small, with a mean birth weight of only 2700 g, and 30% have a birth weight of 2650 g or less (C S Yajnik). Their mothers are short and underweight, with a mean body mass index of only 18. Furthermore, Yajnik's group in Pune find that these small babies have a low muscle mass, small viscera, and a relative excess of fat (C S Yajnik et al)—a body composition particularly likely to lead to insulin resistance. A cohort study by Yajnik's group showed that lower birth weight and higher body mass index in childhood are associated with impaired

BMJ 2001;322:375–6

glucose tolerance in these children (A Bavdekar et al). The fetal origins hypothesis predicts high rates of type 2 diabetes for them later in life. The prevalence of diabetes in India is likely to go on increasing and to constitute a major health burden.

Can fetal growth be improved in pregnancies at risk for fetal growth retardation? Improving the mother's growth and nutrition before pregnancy is the ideal strategy, but animal studies show that more than one generation of improved maternal nutrition may be needed to optimise fetal growth. Later marriage and childbearing would allow Indian mothers to start pregnancy better grown (W P T James and J M Wallace). Only limited evidence exists that nutritional supplements in pregnancy improve fetal growth in undernourished mothers (A M Prentice). Furthermore, the effects of supplements vary according to the stage of pregnancy: giving them early in pregnancy may even worsen fetal growth.

The thrifty phenotype is a paradigm that has stimulated animal as well as human research on fetal growth retardation; its neuroendocrine and metabolic effects; and the possible mechanism by which metabolism, body composition, and growth may be permanently affected. It was widely if not universally accepted by the congress as a model to explain the link between fetal growth retardation and later diseases. Of the existence of that link there is no doubt, and in the 21st century it may matter most in the Indian subcontinent.

Roger Robinson *associate editor, BMJ*

The *BMJ* provided financial support to the congress. RR wrote an introductory chapter to *Fetal and infant origins of adult disease.*[1]

*Papers presented at the congress are indicated here by their authors' names in parentheses. Abstracts will be published in a supplement to *Pediatric Research*, July 2001.

1 Barker DJP, ed. *Fetal and infant origins of adult disease.* London: BMJ Books, 1992.
2 Hales CN, Barker DJP. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 1992;35:595-601.

The protective effect of childhood infections

The next challenge is to mimic safely this protection against allergy and asthma

Papers p 390

Although infectious diseases are by no means defeated, the past 100 years have seen a dramatic decline in some previously common childhood infections. Many serious viral and bacterial infections can now be prevented or treated by vaccination or antibiotics. In contrast, the prevalence of asthma and atopic disease has increased, particularly during the past 30 years. This increase is certainly not accounted for by a change in genetic risk factors: genetically similar populations in East and West Germany had very different rates of asthma before unification (although former east Germany is now catching up with the west[1]). In a landmark study of hayfever, hygiene, and household size in 1989 Strachan proposed that improved hygiene was the factor that explained this rise.[2]

The immunological arguments that underlie this "hygiene" hypothesis can be summarised as follows. Many common viral infections induce a strong protective host response dominated by the production of interferon γ (IFNγ). This type 1 response is more effective at eliminating viruses than the alternative type 2 response (characterised by the production of interleukin 4 and interleukin 5), which promotes IgE production, eosinophilia, atopy, and asthma. Children are born with strong type 2 responses but mature their type 1 responses in the first year or so of life under environmental influence, mainly that of common childhood infections. Children born to atopic parents are slower to do this than those born to non-atopic parents.[3]

Thus, having many older siblings; attending day care at an early age[4]; growing up on a farm and in frequent contact with cattle, poultry, and cats; and having childhood measles[5] and orofaecal infections such as hepatitis A[6] are all helpful (directly or by association) in promoting normal immunological maturation and in preventing atopic disease. By contrast, living in a small family group in hygienic conditions and taking antibiotics in early life[7] may promote the development of asthma and atopy.

In this issue of the *BMJ*, Illi et al show that episodes of uncomplicated common colds (runny nose) during infancy may also protect against episodes of wheezing in later childhood (p 390).[8] Other childhood infections such as herpetic stomatitis, exanthema subitum, and chickenpox also seemed protective. By contrast, episodes of wheezy lower respiratory tract infection were strongly associated with subsequent episodes of wheezing by the age of 7 (odds ratio >6). In other words, children with frequent simple infantile colds are less likely to develop wheezing by the age of 7, while children with wheezy lower respiratory illnesses in the first year are more likely to wheeze later on.

The authors acknowledge the difficulty of showing cause and effect in observational studies of this type. Importantly, no attempt was made to confirm the clinical diagnosis of viral colds by laboratory studies, and the authors were unable to determine whether rhinovirus, coronavirus, or respiratory syncytial virus had different effects. However, the important conclusion is that the risk of a diagnosis of asthma by the age of 7 is reduced by about 50% percent in children with two or more reported episodes of common cold (without associated wheeze) by the age of 1 year.

The challenge before us is to find ways of reproducing the protective effects of early childhood infections, while at the same time reducing the burden of serious (and less serious but still troublesome) infectious diseases. With increasing numbers of effective vaccines, antiviral treatments, and antibiotics and with increasing affluence, how can we prevent the continued rise in asthma and atopic disease? Perhaps different common cold viruses have different effects. Since there is evidence that respiratory syncytial virus bronchiolitis is a risk

BMJ 2001;322:376–7