Saturday 14 May 2005

BMJ

Antioxidants for children with kwashiorkor

Oxidative stress may not explain this deadly disease

Papers p 1109

Protein energy malnutrition is the most deadly form of malnutrition. It is the primary or associated cause of around half of the nearly 11 million annual deaths among children under five, 30 000 each day.[1] The reasons for this tragedy are quite clearly poverty, underdevelopment, and inequality, yet knowing this does not translate into finding correspondingly obvious or immediate solutions.

Clinically, protein energy malnutrition presents broadly as one of two extremes: the severe loss of body weight of marasmus or the oedematous malnutrition of kwashiorkor. Conceptualisation of protein energy malnutrition in this way has some disadvantages in its simplicity, but it does have practical importance and reflects differences in epidemiology, pathophysiology, treatment, and presumably aetiology. Of the two, kwashiorkor is consistently the more lethal, with a high case fatality rate in many areas, and therefore merits special consideration.

Ever since Cicely Williams described the entity known as kwashiorkor in 1935 while working in west Africa, there has been much and sometimes vigorous debate on its pathogenesis.[2 3] Why is it that among children destined to become malnourished some develop kwashiorkor while others develop marasmus? What are the determinants? Remarkably little research has been conducted over the past several decades on this question, despite the enormous practical implications of the answer. Painfully slow progress over the same period in reducing the global prevalence and childhood mortality of malnutrition reflect this lack of evidence.

Several insults have been proposed as principal causes of kwashiorkor including dietary protein deficiency, aflatoxins in food, and depressed cellular protein synthesis reinforced by infection. Nearly 20 years ago Golden et al proposed the free radical theory as a unifying hypothesis, which has become a main focus of conjecture.[4 5] This theory proposes that kwashiorkor arises from excessive noxious insults, resulting in the generation of sufficient reactive oxidative free radicals to exceed the host's antioxidant capacity. An accumulating body of evidence, albeit indirect, lends substantial support for this concept.[6 7] Various studies have shown that children with kwashiorkor, when compared to marasmic or normal controls, have greater concentrations of biomarkers of oxidative stress and damage as well as lower blood concentrations of antioxidants. Furthermore, clinical resolution of kwashiorkor coincides with the return to normal of these markers.

It is in this context that the study of Ciliberto et al in the current issue of the *BMJ* is most welcome.[8] This study examined the impact of an antioxidant cocktail as a possible preventive treatment for kwashiorkor in children in a highly endemic area of Malawi and, notably, found no protective effect. Although these results may put a damper on the antioxidant hypothesis, it would be premature to discard the theory altogether. The specific antioxidants used in the Ciliberto study are known to have a high relative antioxidant capacity, but the amounts taken by the children may have been insufficient to overcome high oxidative stress and prevent kwashiorkor. Since neither antioxidant capacity nor oxidative stress was measured, an element of doubt about the adequacy of the antioxidant mix or dose is reasonable. Moreover, the study did not assess the children's HIV status, which may have contributed to or affected their responses to oxidative stress. More than 20% of Malawian children in hospital with kwashiorkor have HIV infection; indeed, kwashiorkor has been described as the final common pathway for children with AIDS.[9]

The aetiology of kwashiorkor is clearly multifactorial and includes in varying proportions food insecurity, inadequate weaning and other feeding practices, infection, and, the current study notwithstanding, possibly oxidative stress. The relative contribution of the elements that create the "perfect storm" of kwashiorkor may not be universal among different groups of children. That said, the results of this new study provide evidence that antioxidants might not play a central decisive role as originally proposed.[5] They also serve to emphasise that 20 years is far too long to test the leading hypothesis for a condition that affects so many children with such devastating consequences.

George J Fuchs *professor of pediatrics*

University of Arkansas for Medical Sciences, Arkansas Children's Hospital, 800 Marshall Street, Little Rock, AR 72202 USA (fuchsgeorgej@uams.edu)

Competing interests: None declared.

1 World Health Organization. *Nutrition for health and development: a global agenda for combating malnutrition.* Geneva: WHO, 2000.
2 Williams CD. Kwashiorkor: a nutritional disease of children associated with a maize diet. *Lancet* 1935;229:1151-2.
3 Waterlow J. Causes of oedema and its relation to kwashiorkor. In: Waterlow J, ed. *Protein-energy malnutrition.* London: Edward Arnold, 1992:146-63.
4 Golden MHN. The consequences of protein deficiency in man and its relationship to the features of kwashiorkor. In: Blaxter KL, Waterlow JC, eds. *Nutritional adaptation in man.* London: John Libby, 1985:169-88.
5 Golden MHN, Ramdath D. Free radicals in the pathogenesis of kwashiorkor. *Proc Nutr Soc* 1987;46:53-68.

BMJ 2005;330:1095–6

6 Krawinkel M. Kwashiorkor is still not fully understood. *Bull WHO* 2003;81:910-11.
7 Waterlow J. Cell membranes and free radicals. In: Waterlow J, ed. *Protein-energy malnutrition*. London: Edward Arnold, 1992:136-45.
8 Ciliberto H, Ciliberto M, Briend A, Ashorn P, Bier D, Manary M. Antioxidant supplementation for the prevention of kwashiorkor in Malawian children: randomised, double blind, placebo controlled trial. *BMJ* 2005;330:1109-11.
9 Brewster DR, Manary MJ, Graham SM. Case management of kwashiorkor: an intervention project at seven nutrition rehabilitation centres in Malawi. *Eur J Clin Nutr* 1997;51:139-47.

The fetal origins hypothesis—10 years on

Events before birth remain important, but we need to consider later modifiers too

Papers p 1115

Epidemiological studies have largely contributed to our understanding of the natural history of coronary heart disease. Although clinical manifestations of the disease usually become evident in adult life, early signs are recognisable in childhood. The discovery that individuals who develop coronary heart disease grow differently during early life has led to the recognition of new developmental models for the disease. In 1995 David Barker wrote: "The fetal origins hypothesis states that fetal undernutrition in middle to late gestation, which leads to disproportionate fetal growth, programmes later coronary heart disease."[1] Now, 10 years later, the importance of events before birth for lifetime health has been confirmed in many populations.[2–4] In humans, birth size serves as a marker of the intrauterine environment. Considering that birth size is just one snapshot of the trajectory of fetal growth it is fascinating that long term health outcomes are predicted by the body size of the newborn.

The association between birth size and cardiovascular morbidity is largely modified by growth later in life. The highest risk of coronary heart disease is seen among individuals who were born small and became heavier during childhood.[4–6] Most previous studies have been done in males but in this issue we have a paper based on findings from the nurses' health study following up over 66 000 female nurses.[7] This study confirms the inverse associations between birth weight and risk of cardiovascular disease in women. Risk of coronary heart disease was highest among women who were smaller at birth and who grew up to be heavier adults. The risk of coronary heart disease was not elevated among women with lower birth weight who remained relatively lean in adult life. Obviously the consequences of becoming heavier in childhood and adulthood are conditioned and modified by growth in the womb and do not depend solely on the absolute level of body weight attained. After an intrauterine lesion, regulatory mechanisms may maintain homoeostasis for years until further damage because of obesity or other influences initiates a self perpetuating cycle of progressive functional loss leading to disease. Therefore we need to recognise the importance of modifiers working later in life.

Not only fetal growth but also growth during early childhood is a major player in the game of long term health outcomes.[8 9] The most unfavourable growth pattern seems to be thinness at birth and during early childhood followed by a rapid increase in body weight. These observations are globally of extreme importance since malnutrition in early life is a widespread health problem. The impact of the problem is easy to understand knowing that approximately a third of the world's children suffer from protein energy malnutrition. Stunted children are at high risk of becoming overweight. The public health implication of this is naturally to prevent excess childhood and adult weight gain, with the intervention especially targeted at those born small.

Although the evidence for an association between impaired fetal growth and increased risk of coronary heart disease is compelling, it is premature to make policy recommendations in order to increase birth weight. Interventions to increase birth weight could even be harmful. Many of the current findings have emerged from historical cohorts. Future studies should be long term prospective studies collecting biological samples to increase our understanding of the underlying processes. In the future, individual tailoring of lifestyle and pharmaceutical interventions according to early growth patterns and genetic setting may maximise benefits in the prevention of cardiovascular disease and other non-communicable diseases.

We are beginning to see that adult degenerative diseases are associated with different patterns of growth—the same disease may even originate through more than one pathway.[10] Unfortunately what optimal growth is and how this can be achieved is not clear. Obviously this is also related to the measured outcome. The development of most non-communicable diseases entails several interactions, including genetic ones.[11] From a public health point of view we need to keep in mind that adult diseases are not programmed as such but the tendency towards a disease is programmed. The early risk factors are to a large extent modified by a huge range of factors working during the whole life course and lifestyle matters from the cradle to the grave.[12] Adult diseases can therefore best be focused on from a life cycle perspective. The promise of the fetal origins paradigm is that attending to the health of women of reproductive age will have profound impact on the wellbeing of their offspring. The importance of this issue closely parallels WHO's *World Health Report 2005*—"Make every mother and child count."

Competing interests: None declared.

Johan G Eriksson *head of unit*

National Public Health Institute, Department of Epidemiology and Health Promotion, Diabetes and Genetic Epidemiology Unit, Mannerheimintie 166, 00300 Helsinki, Finland (Johan.Eriksson@ktl.fi)

1 Barker DJ. Fetal origins of coronary heart disease. *BMJ* 1995;311:171-4.
2 Stein CE, Fall C, Kumaran K, Osmond C, Cox V, Barker DJP. Fetal growth and coronary heart disease in South India. *Lancet* 1996;348:1269-73.
3 Rich-Edwards JW, Stampfer MJ, Manson JE, Rosner B, Hankinson SE, Colditz GA, et al. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *BMJ* 1997;315:396-400.

BMJ 2005;330:1096–7