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Invited commentary

Growth retardation and stunting of children in developing countries

The growth of infants and children throughout the world is related to the socio-economic environment in which they live. Children from developing countries grow more slowly and achieve a shorter adult height than those from wealthier regions (Tanner, 1986). Even within countries, offspring from more affluent families grow faster and achieve greater stature than their poorer neighbours. In addition, many studies have shown that growth rates and final stature improve when families migrate from poor, developing countries, to richer, developed regions, confirming that such differences in growth performance are not genetically determined (with rare exceptions, e.g. the African pygmies). We are therefore left with the conclusion that the poor growth and consequent high levels of stunting seen in so many developing countries must be the result of adverse environmental and/or living conditions.

Of the various possible factors, dietary adequacy and disease prevalence are generally believed to have the greatest impact on growth. Perhaps because stunting is regarded as a form of malnutrition, most investigations into the cause of poor growth in developing countries have concentrated on nutritional availability and dietary composition: early studies were concerned with protein and energy content whilst more recent ones have concentrated on micronutrient adequacy. Many food-supplementation trials aimed at improving growth have been undertaken in several different parts of the world, but outcomes have not been very impressive. In a few studies, small improvements have been demonstrated (Schroeder *et al.* 1995), but in others no change was detected, growth remained poor and children still became stunted despite plentiful supplies of high quality food (Prentice, 1993). The inevitable conclusion to be drawn from such studies is that, in general, stunting of children in developing countries cannot be fully explained on the basis of dietary inadequacies.

If growth retardation cannot be attributed primarily to nutrition, then surely it must be disease-mediated. The prevalence of common infectious diseases is undoubtedly much greater in poor, developing countries than it is in westernized societies, but attempts to relate growth, particularly growth in height, to disease prevalence within communities, have also not been convincing. The frequent episodes of diarrhoeal disease suffered by many children in the developing world have often been assumed to be a cause of poor growth. However, although acute diarrhoeal episodes do result in short-term loss of weight, they are usually followed by a period of catch-up growth, so that in the long term, the prevalence of diarrhoea is not associated with deficits in either height or weight (Briend *et al.* 1989). Similarly, respiratory diseases and other infective childhood illnesses have been found to have only small or no long-term effects on growth in height (Bhan *et al.* 2001). This inability to attribute long-term growth faltering to either nutritional factors or overt clinical disease has led to speculation about possible nutrition–disease synergisms and the role of sub-clinical disease states.

Undoubtedly, the aetiology of stunting is complex and a full understanding of its cause(s) requires more detailed investigations into the physiological mechanisms by which environmental factors may promote or suppress growth. Of particular interest is the role of the gastrointestinal tract and particularly the mucosa of the small intestine as this represents a major interface between the body and the environment. A single layer of cells, the enterocytes, which line the mucosa, must be able to absorb nutrients, but must also act as a barrier to prevent environmental toxins and micro-organisms from gaining access to the body. Clearly, environmentally induced damage to the mucosa could compromise both nutrient uptake and barrier function, both of which could lead to impaired growth (Lunn, 2000), and this is the focus of the current paper by Goto *et al.* (2002).

It has been known for many years that intestinal mucosal morphology varies with geographical location. Intestinal biopsy studies in the 1960s and 70s demonstrated a high prevalence of altered villus architecture, partial villus atrophy and lymphocytic infiltration of the lamina propria in asymptomatic adult residents of tropical areas of the world (Anon, 1972). These abnormalities were seen not only in the indigenous populations of these countries, but they were also found in long-term travellers or migrants to the tropics. The condition, termed tropical enteropathy, was reversible and the mucosa gradually returned to normal following migration back to a more temperate climate. Today, the prevalence of tropical enteropathy remains very high in most parts of the developing world, but is now believed to be associated with living in a poor, unhygienic and unsanitary environment rather than the climate. In fact it is now thought to occur through chronic exposure of the small intestinal mucosa to a variety of food- or water-borne micro-organisms, viruses, bacteria and protozoans which cause repeated, frequent sub-clinical episodes of enteric infection (Menzies *et al.* 1999).

Similar lesions of the small intestinal mucosa of severely malnourished children were also first described the 1960s (Brunser *et al.* 1968), but in this case, the 'enteropathy of malnutrition' was assumed to occur as a result of a

reduced rate of enterocyte renewal due to a poor or inadequate diet, i.e. it was believed that the enteropathy occurred as a consequence of the child's malnutrition. It is now thought far more likely that the aetiology of this childhood enteropathy is similar to tropical enteropathy of adults, i.e. it is caused by chronic exposure to enteric pathogens, and moreover, that the enteropathy may be an important cause of malnutrition, particularly stunting, rather than a consequence (Lunn, 2000).

The paper by Goto *et al.* (2002) in the present issue of the *British Journal of Nutrition* describes an investigation in which small intestinal mucosal function and integrity was assessed using the dual-sugar intestinal permeability test. The test is non-invasive and, as demonstrated in the study, can be used under field conditions. In performing the test, subjects are given measured oral doses of two probe molecules (usually lactulose with either mannitol or rhamnose), dissolved in water, and all urine passed during the following 5 h is collected. The theory behind the test is that mannitol (or rhamnose), being a monosaccharide, is small enough to pass through the numerous water-filled pores of the enterocyte cell membranes (Travis & Menzies, 1992). Thus, the proportion of the dose that is taken up gives an estimate of the total absorptive surface area of the small intestine. Lactulose, a disaccharide, is too large to pass through the pores of healthy enterocytes and in a normal intestine only very small amounts are absorbed, probably via paracellular routes between the cells. However, in a damaged mucosa larger amounts of lactulose permeate because of increased leakiness through and around the damaged enterocytes. Both probes pass from the mucosa into the blood from where they are quantitatively excreted into the urine by the kidneys. Consequently, the amount of each probe excreted in the urine is a measure of the amount absorbed across the mucosa. In situations of mucosal damage, lactulose uptake can be expected to rise and monosaccharide absorption to fall, thus the permeability ratio, i.e. the ratio of their recovery in the urine, provides a sensitive overall index of mucosal status. In addition, inclusion of lactose in the dose allows an estimation of intestinal lactase activity, an enzyme essential for the digestion breast-milk lactose (Travis & Menzies, 1992; Northrop-Clewes *et al.* 1997).

The work of Goto *et al.* (2002) reports that intestinal permeability levels are elevated in stunted children in Nepal. They also found raised lactose:lactulose ratios in the urine of breast-feeding children, which suggests that intestinal lactase activity of the mucosa was decreased, causing partial maldigestion of lactose (Northrop-Clewes *et al.* 1997). However, in the study by Goto *et al.* (2002), neither variable was related to indices of nutritional status, i.e. weight- and height-for-age z-scores. This may have been because of the rather wide age range of subjects, i.e. 6–60 months, and the mild degree of stunting. The particularly high permeabilities observed with *Giardia* infection, but lack of effect of helminth parasites confirms and adds to the sparse amount of data on this subject (Northrop-Clewes *et al.* 2001). Overall, the study provides further evidence of the presence of mucosal enteropathy in largely asymptomatic, stunted children living in a poor environment.

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