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NUTRITION, INFECTION AND CHRONIC TROPICAL ENTEROPATHY IN AFRICAN INFANTS

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INTRODUCTION

Under optimal conditions the interactions between food and the gut microflora act in synergy to aid host defences and modulate systemic immunity hence creating 'The Golden Triangle' that is the theme for this symposium. But when this symbiosis breaks down the interactions can become malignant and might better be described as a 'black triangle'. This struggle between the human host and pathogenic enteric organisms has been the norm over most of human evolution and remains a major challenge for the majority of the world's infants raised, as they are, in unhygienic conditions. This paper uses our research from a rural population in The Gambia as a case study to describe the struggles between the human host and its pathogens under such conditions.

GROWTH FAILURE

The typical pattern of infant growth in rural Gambia is illustrated in Figure 1. Babies are typically born small but then show rapid catch-up growth during the first 3 months of life when fully breast-fed and generally free from infections. This catch-up is so successful that at 3 months of age the population average is close to western growth norms. Thereafter there is a precipitate deterioration in growth so that by the end of infancy the population average Z-score is close to –2.0 for weight, -1.2 for length and –2.3 for head circumference. This represents the average growth pattern across all calendar months and is strongly modulated by seasonal variation (*McGregor* et al., 1961). During the rainy season (July-October) growth virtually stops in many infants as a consequence of a sharp increase in infectious diseases including diarrhoea (*Rowland* et al., 1977), and a deterioration in maternal care practices due to the fact that mothers have to work long hours in the fields and frequently leave their infants with a young nursemaid or a grandmother who is no longer able to work. The effects of this are illustrated in Figure 2, which shows the seasonal variation in the number of severely malnourished infants referred by paediatricians to a local therapeutic feeding centre.

The issue of when to start introducing complementary foods has been described as the 'weanling's dilemma' by *Rowland* and colleagues (1978). Weaning foods in sub-Saharan Africa typically have a very low energy and nutrient density, and frequently have

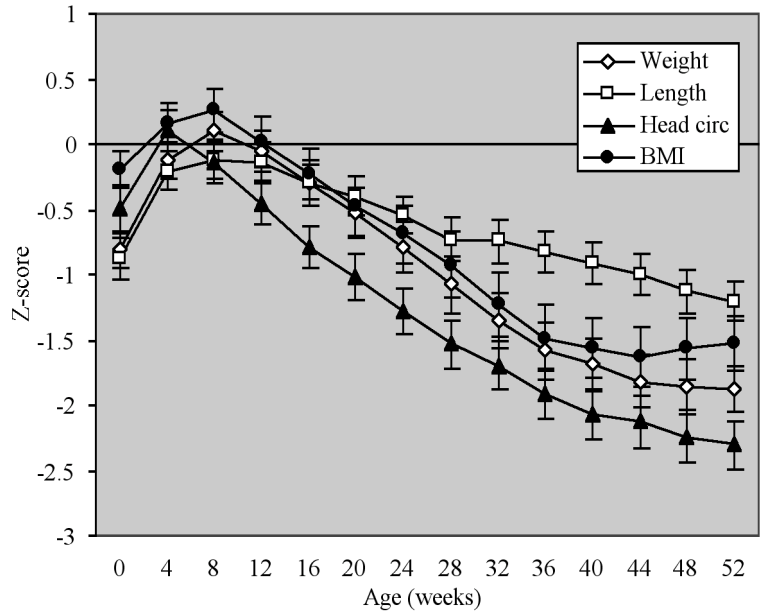

Figure 1: Early growth faltering in Gambian infants. Data from 138 Gambian infants assessed longitudinally and expressed as Z-scores relative to the UK 1990 standards. Reproduced with permission from *Collinson* et al. (2005).

high levels of bacterial contamination (*Barrell* and *Rowland*, 1979). The dilemma therefore is that if mothers introduce weaning foods too early they risk causing diarrhoea and inhibiting their own lactational performance, but if they introduce them too late their infant's energy needs may have started to exceed their milk energy supply. This dilemma is faced by all mothers but is much more acute in poor communities with few facilities for hygienic food preparation where weaning foods are likely to be contaminated. The hazards associated with this transition frequently result in the initiation of a vicious cycle of malnutrition and chronic intestinal infections as illustrated in Figure 3.

GASTROINTESTINAL INFECTIONS

Various bacterial and viral pathogens have been implicated as etiologic agents for diarrhoea in The Gambia (*Lloyd-Evan*s et al., 1983; *Sullivan* et al., 1990, 1991a; *Rowland* et al., 1980; *Billingham*, 1981; *Goh Rowland* et al., 1985). Some have been found to be significantly associated with diarrhoea while others have been seen to be equally prevalent in asymptomatic children. Bacterial contamination of the jejunum was predominant in a small series of malnourished children with diarrhoea (*Heyworth* and *Brown* 1975).

The role of giardiasis has been investigated in a study in urban Gambian children and was found more commonly in control stools rather than those of diarrheic stools (*Goh Rowland* et al., 1985). However, the prevalence was significantly higher in children with chronic diarrhoea and malnutri-

Figure 2: Seasonal pattern of severe malnutrition reflected in the monthly admissions to a therapeutic feeding centre.

tion compared to healthy controls (45% vs. 12%), but not when compared with marasmic controls (27%) (*Sullivan* et al., 1991a). In a longitudinal community study on giardiasis (measured by serology) and weight gain of rural Gambian infants, elevated titres of *Giardia*-specific IgM antibodies were associated with decreased weight gain in the 2 week period prior to serological conversion (*Lunn* et al., 1999). High *Giardia*-specific IgM was also associated with elevated intestinal permeability values and decreased

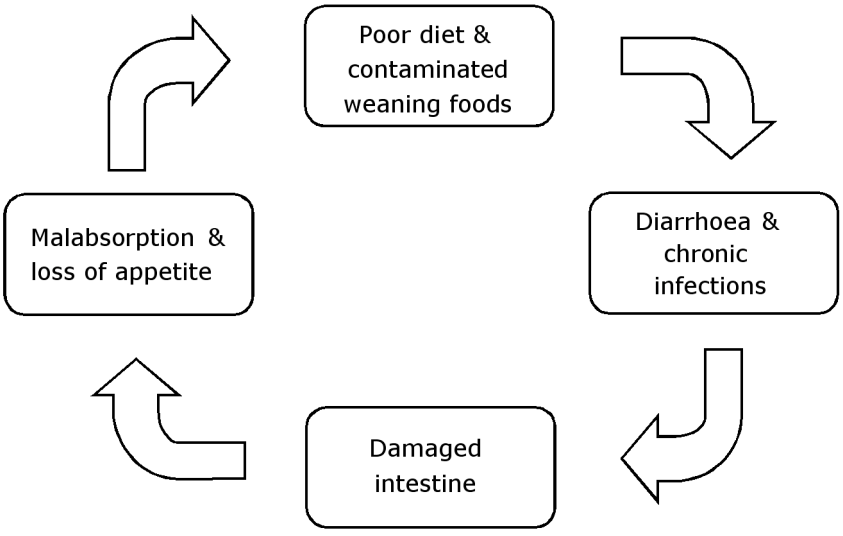

Figure 3: The vicious cycle of malnutrition and chronic infection typical of poor communities in developing countries.

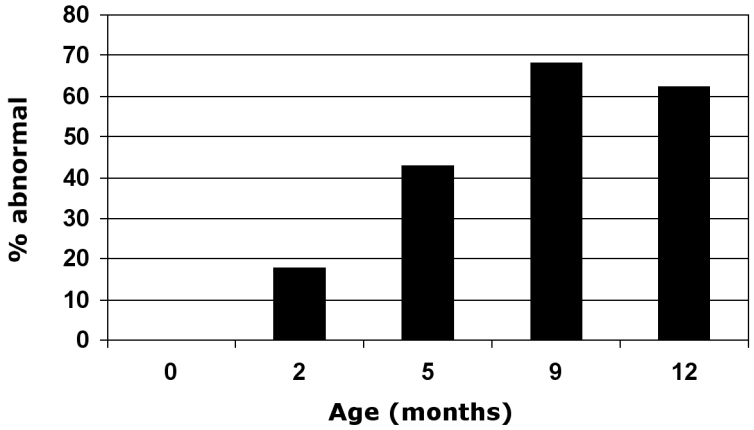

Figure 4: Raised inflammatory α-1 acid glycoprotein in rural Gambian infants. (Data from 197 infants studied longitudinally (*Darboe* et al., unpublished). The normal cut-off is ≤ 1g/l.)

mannitol absorption (*Lunn* et al., 1999). However, the mean IgM titres per child over the entire study period did not predict differences in long-term growth or intestinal permeability. In a community-based study, it was also shown that although intestinal inflammation (as measured by faecal neopterin) was inversely associated with growth, the presence of giardiasis was neither associated with poor growth or poor intestinal permeability (*Campbell* et al., 2004). It appears that in the Gambian setting, giardiasis is more prevalent in chronic diarrhoea and malnutrition, but its role in modulating the acute growth of infants seems to be less clear.

A study on *Helicobacter pylori* infection on severely malnourished Gambian children was probably the first study in African children (*Sullivan* et al., 1990). This showed that close to half the children aged between 40 to 60 months had serologic evidence for infection. Half of the children with chronic diarrhoea and malnutrition were positive as compared to a quarter of healthy controls and undernourished children. In a later study using the ^{13}C-urea breath test, it was shown that acquisition of *H. pylori* infection may occur before 3 months of age as 20% of the 3-month-old infants were positive (*Thomas* et al., 1999). An analysis of longitudinal growth data and serial breath tests demonstrated that children who acquired *H. pylori* earlier ended up shorter, lighter and thinner than their uninfected peers (*Dale* et al., 1998). It has been proposed that early *H. pylori* causes a transient hypochlorhydria and thereby increases the likelihood of enteric infection thus compromising intestinal function and nutrition. *H. pylori* infection may serve to reduce the mucosal defences and allow further colonisation of the small intestine with pathogens (*Dale* et al., 1998). It is noteworthy that studies in developed countries have shown an association between *H. pylori* infection and increased intestinal permeability (*Borch* et al., 1998, *Di Leo* et al., 2005).

Figures 4 and 5 illustrate very recent data on abnormal levels of α-1 acid glycoprotein (used as a general marker of infection) and *H pylori* infection among 197 infants studied longitudinally, and demonstrate that the pathologies described by earlier workers,

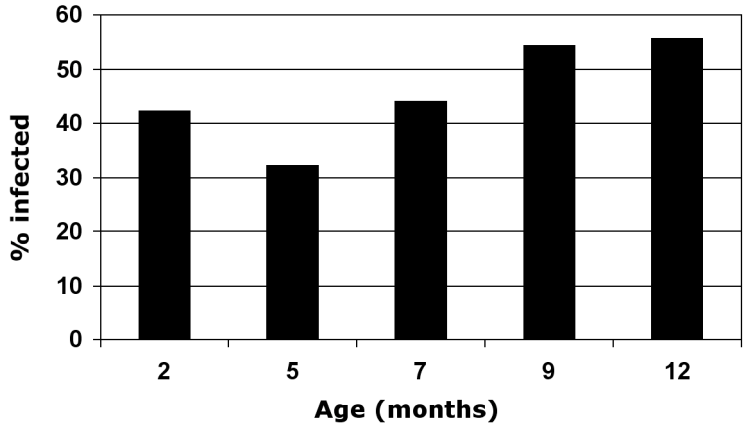

Figure 5: Proportion of rural Gambian infants with *Helicobacter pylori* infection assessed by the urea breath test. Data from 197 infants studied longitudinally (*Darboe* et al.,, unpublished).

as summarised above, are still highly prevalent despite considerable improvements in health care and major reductions in mortality (*Rayco Solon* et al., 2004).

CHRONIC ENVIRONMENTAL ENTEROPATHY

Persistent gastroenteropathy, as characterized histologically by small-intestine mucosal villous shortening and broadening, crypt hyperplasia, increased crypt depth, and lymphocyte infiltration into the lamina propria and epithelium (*Sullivan* et al., 1991b, 1992; *Campbell* et al., 2003, *Solon* et al., 2006), is a feature of many Gambian children. Previous research has established this inflammatory condition to be strongly associated with growth failure. First described in 1962, persistent enteropathy was found to affect individuals throughout the tropics, in Africa, Asia, South America and the Caribbean (*Thomas* et al., 1976, *Brusner* et al., 1987). For this reason it acquired the name 'tropical enteropathy'. The condition was particularly observed in those living in less developed, or more contaminated, environments of the tropics. It was later shown that people living in temperate areas may develop similar histological and functional changes if living in environments with similarly high levels of microbiological pathogens. For these reasons the expression 'chronic environmental enteropathy' is now accepted as a more accurate description of the condition than 'tropical enteropathy'.

Associated functional changes include subclinical malabsorption of fat and an increased mucosal permeability. The latter is demonstrated by markedly and consistently raised lactulose:mannitol (L:M) ratios in the dual-sugar permeability test (DSPT) towards later infancy (see Figure 6). Raised L:M ratios have also been described in children in several other parts of the developing world. The DSPT assesses both gut integrity and absorptive capacity, and has been used in numerous studies characterising the aetiology of growth failure in The Gambia (*Lunn* et al., 1981) and elsewhere (*Goto* et al., 1999, 2002).

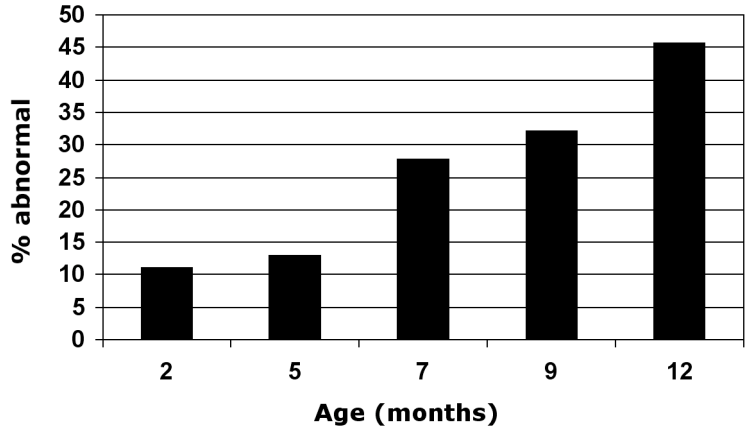

Figure 6: Proportion of rural Gambian infants with abnormal gut permeability assessed by the lactulose:mannitol test. Data from 197 infants studied longitudinally (*Darboe* et al., unpublished). The normal cut-off for the lactulose:mannitol test was set at 0.3.

Two sets of immunohistologic studies have been performed in The Gambia. These are consistent with past biopsy studies in marasmus and kwashiorkor done in other developing countries over the past four decades; in particular they describe a wide spectrum of crypt hyperplasia and villous atrophy across cases. In addition, immunohistology revealed intraepithelial lymphocyte infiltrates in the surface villi and crypts (*Sullivan* et al., 1991b), predominantly of the CD8+ phenotype. Follow-up studies on rehabilitated children showed that with treatment, the crypt cell compartment increased in size, but there was no corresponding increase in epithelial volume (*Sullivan* et al., 1992). T-cells are known to play an important role in other inflammatory enteropathies such as Crohn's disease and coeliac disease (*MacDonald* et al., 1999). The most recent biopsies done in The Gambia (*Campbell* et al., 2003) have demonstrated a generalised cellular hyper-responsiveness and a cytokine profile biased towards proinflammatory cytokines. The intestinal infiltrate was dominated by T Cells (CD3), γδ T cells, activated T cells (CD25), activated cytotoxic T cells (perforin+) and elevated levels of TNFα, IFNγ, and TGFβ, but not IL-10. TGFβ:TNFα and TGFβ:IFNγ ratios were higher with better nutritional status. L:M ratios were increased (more gut damage) in children with more T cells and activated cytotoxic T cells, and decreased with more B cells (CD19).

The immunohistological studies contradict the commonly held belief that malnutrition is associated with an immunosuppressed state, and instead suggest that both lymphocyte activation and ineffective enterocyte development play a significant role in chronic environmental enteropathy and malnutrition. These findings support the view that malnutrition is not necessarily accompanied by severe T-lymphocyte deficiency, and that T-lymphocyte dysregulation may be present (*Morgan*, 1997).

THERAPEUTIC INTERVENTIONS AIMED AT TREATING CHRONIC ENVIRONMENTAL ENTEROPATHY

Under optimal conditions affected children who develop severe malnutrition will be admitted to a specialist treatment centre and treated according to the formalised WHO guidelines for the Treatment of the Severely Malnourished Child (*WHO*, 1999). If implemented properly such therapy can greatly reduce the normally high levels of mortality associated with severe malnutrition (*Ashworth* et al., 2004). But as with many clinical syndromes the greatest burden of disease is associated with less severe forms since they affect a much larger proportion of children. In The Gambia we have tested a number of preventive and therapeutic population-based interventions aimed at reducing the enteropathy and hence at preventing the widespread growth faltering. These have included supervised protein-energy supplementation between 3-6 months, and interventions with glutamine, zinc, early high-dose vitamin A, probiotics and multiple micronutrients. To date none of these have been successful and we will shortly be embarking on a randomised controlled trial of long-chain N3 polyunsaturated fatty acids (PUFAs) administered daily to infants 3-9 months of age with the aim of suppressing the persistent and inappropriately vigorous inflammatory response within the mucosal epithelium.

Ultimately it is recognised that a whole package of interventions including clean water supplies, better hygienic conditions and maternal education will be required in order to fully rectify the growth failure and the attendant developmental disadvantages suffered by so many infants in the developing world.

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