Leading article – Tropical infection of the gastrointestinal tract and liver series

Paediatric problems in tropical gastroenterology

After the introduction of oral rehydration therapy for the treatment of acute diarrhoea in infancy and childhood, the case management of such diarrhoea has considerably improved both in hospital and at home. This has in tropical communities led to a sharp decline in the numbers of deaths from diarrhoea. Indeed fewer children are being seen with severe dehydration and the World Health Organisation believe 90% of all deaths from diarrhoea in children may be prevented.

Chronic diarrhoea has emerged, however, as an important problem as a result of this improvement in mortality and in particular, persistent diarrhoea – that is, diarrhoea that begins acutely but persists, continuing beyond two weeks after the onset of the acute diarrhoea. The causes of this symptom are many and the best treatment for persistent diarrhoea is not yet agreed.

Acute diarrhoea

ACUTE INFECTIVE DIARRHOEA

Despite improved treatment with oral rehydration therapy, acute diarrhoea of infective origin remains an important problem in the developing world. A two year study of this problem in children aged less than three years in China, India, Mexico, Myanmar (Burma), and Pakistan has been published.¹ A total of 36 400 children with diarrhoea were studied and 3279 age matched controls. Sixty per cent were boys and roughly 60% were aged less than one year.

Only three infectious agents were found to be consistently or substantially increased in the children with diarrhoea. These were: rotavirus (16% diarrhoea, 2% controls), shigellae (11% diarrhoea, 1% controls), and enterotoxigenic *Escherichia coli* (16% diarrhoea, 5% controls).

Rotavirus is clearly the most frequently identified cause of acute diarrhoea in childhood in tropical communities, just as it is temperate communities.

Its peak age in tropical countries is between the age of 6 and 12 months, although it can occur in younger infants.

In tropical communities the typical peak associated with cooler weather is not seen and sometimes there is no seasonal trend at all, suggesting that it is present all the year round, with low level transmission maintaining the infection in the community.²

While it is clear that rotavirus is spread by the faecal-oral route, its persistence in developed communities where there is good sanitation and a high level of breast feeding, suggests that airborne and droplet transmission are also possible.

PREVENTIVE METHODS

The present problem of high infantile diarrhoeal mortality in the developing world has important analogies with the high and sometimes rising infant mortality from diarrhoeal disease in countries such as Britain, Australia, and New Zealand that occurred at the beginning of the twentieth century.

This occurred despite the development of clean water and vastly improved sanitation. Newman,³ writing in 1906, stated that infantile diarrhoea mortality was a disease of urban deprivation. He found that infantile diarrhoeal diseases were: (a) very much more fatal in urban rather than rural districts; (b) more dangerous to boys than girls; (c) more severe in first year of life; (d) aggravated by bad housing, poverty, artificial feeding, and domestic insanitation.

Infantile diarrhoea was regarded as a 'filth illness' and this led to the demand for improved housing and domestic environment. Rather surprisingly, once *E coli* and other infectious agents were recognised years later, this in fact took the pressure off the Public Health Authorities to improve housing.⁴

Oral rehydration therapy, despite its enormous value in preventing death of infants does not prevent infective diarrhoea. Its cheapness and effectiveness must not, however, deflect governments from seeking to achieve better housing and a clean domestic environment.

In fact, questions have been raised concerning the health benefits of the provision of clean water and good sanitation in developing countries. There is real evidence of benefit, however, when good epidemiological studies are used.⁵ Recently a meta-analysis of the effects of improved water supply and sanitation upon diarrhoea and worm infestation was undertaken.

Provision of sanitation facilities decreased both diarrhoea morbidity and mortality and also the severity of hookworm infection. Better water quality was less important for the control of diarrhoea.⁶

In 1906 Newman attributed the increased infantile mortality in great part to the result of a rise in artificial feeding of infants. He stressed the dangers of contaminated milk and the virtues of breast feeding. However, he believed maternal ignorance was overall an important factor. He recommended an intensive programme of maternal education. This was achieved by the rise of the Infant and Child Welfare Movement.

Indeed the promotion of breast feeding, plus the provision of a clean domestic environment, had a rapid and dramatic effect on infantile diarrhoeal mortality. All this was achieved without the bacteriological proof that infantile diarrhoea was infective in origin, but with the epidemiological evidence that it was spread by infection.

Breast feeding has clearly been established to be a most important factor in protection against enteric infection. In Britain this was established at the end of the nineteenth century by E W Hope, Medical Officer of Liverpool.⁷ He calculated from epidemiological studies in Liverpool in the period 1884 to 1886 that for every 1000 infants under 3 months, breast fed, 20 died of epidemic diarrhoea each year compared with 1000 infants under 3 months, artificially fed, where 300 died. A recent study from Britain reaffirms the protective effect of breast feeding against infection.⁸ Most recent studies, however, concerning the protective effect of breast feeding came from developing

countries^{9 10} where infective diarrhoea is now a far more important problem.

While the general protective effect of breast feeding has clearly been established it has been noted that serious episodes of rotavirus infection may occur in breast fed infants.¹¹ Nevertheless, breast feeding does have a beneficial effect and this has been shown by lessening the severity of infection in hospital acquired infection.¹²

Recently Yolken *et al*¹³ have investigated the mechanisms for breast milk mediated protection against rotavirus infection. They found, a mucin in human milk that can inhibit replication of rotavirus both in vitro and in vivo. Variation in milk mucin glycoprotein levels may be associated with different levels of protection against infection with gastrointestinal pathogens.

The recognition of the heterogeneity of infective agents is a stumbling block for the development of a simple immunisation strategy, although as the study of Huilan *et al* makes clear, there seem to be but three principal pathogens in the developing world.

Promotion of breast feeding probably remains the single most important strategy for the prevention of infantile diarrhoea. Even though it does not completely prevent diarrhoea, especially rotavirus diarrhoea, it has long been known to significantly reduce the mortality of infective diarrhoea.

The most effective way to prevent acute infantile diarrhoea and its mortality is through the mother's role in infant nurture.

Chronic diarrhoea

Postenteritis syndrome and cows' milk allergy in infancy and early childhood are important problems in the developing world. Until comparatively recently the importance of these problems in such communities has not been widely recognised.

The postenteritis syndrome is the clinical syndrome when a child who has had an attack of acute gastroenteritis subsequently has intermittent or chronic diarrhoea for more than two weeks with or without failure to gain weight after the return to a normal diet. In clinical practice two main groups of problems cause delayed recovery after acute gastroenteritis in infancy. Firstly, there is an acute intolerance to the increasing concentration of milk; and secondly, there is a more chronic problem with persistent diarrhoea and failure to thrive.

Most often acute gastroenteritis is an acute self limiting illness and after oral rehydration therapy and the infant's usual cows' milk based feeding formula there is full recovery. Some looseness of stools may persist for some days. There is, however, no worsening of diarrhoea, return of vomiting or further risk of dehydration and weight gain is satisfactory provided there is adequate energy intake. Thus there is an uneventful recovery.

In some infants recovery is delayed. This may result from an intolerance to milk. When such delayed recovery occurs up to two weeks after the start of oral rehydration therapy this is probably a part of the natural history of the gastrointestinal infection as most cases of gastroenteritis, especially those of viral origin, are associated with pathogen excretion in the stools for no more than 10 days to a fortnight. Hence during this period any clinical problem with relapse of symptoms may be embraced by the umbrella term delayed recovery. Once two weeks have elapsed then persistence of symptoms must be regarded as being part of the postenteritis syndrome. This then must be regarded as a problem extending beyond the expected period of spontaneous recovery.

It must be remembered, however, that in the cases of some bacterial syndromes of gastroenteritis, for example

Figure 1: Electron micrograph showing E coli 0114 adhesion with microvillous effacement and pedestal formation.

shigellosis, the natural history of the disease may often extend for several weeks.

Postenteritis enteropathy in childhood

Postenteritis enteropathy may be defined as persistence of a small intestinal mucosal damage – that is, enteropathy beyond the natural history of an acute gastrointestinal infection. In practice this is taken to be more than two weeks after the onset of acute diarrhoea in most cases.

AETIOLOGY

Postenteritis enteropathy may result from the following factors: (a) persistent infection with the original infectious agent; (b) re-infection with another pathogen or pathogens; (c) sensitisation of food antigens causing persistence of small intestinal mucosal damage.

How important is small intestinal enteropathy in pathogenesis of such chronic diarrhoea in infancy in the tropics?

There has in recent years been some reluctance to use small intestinal biopsy as an investigative tool in developing countries and it has not been used as freely as it has been in temperate countries.

It is only by doing small bowel biopsies within a clinical research unit that the true nature of the various syndromes

Figure 2: Transmission electron micrograph showing cryptosporidium adhering to the brush border with loss of microvilli and formation of attachment organelle. (Reprinted from Gut 1993; 33: 1057–61.)

of chronic diarrhoea and malnutrition be unravelled. Clearly the indiscriminate use of small bowel biopsy in developing countries is not advocated. In developed countries the use of small intestinal biopsy combined with food elimination diets and food challenges as well as detailed bacteriological, viral, and parasitic investigations has permitted the clinicopathological spectrum of disease to be established.¹⁴ It is probable that this may vary greatly from community to community.

In India using this approach it is clear that in the north, coeliac disease is an important cause of this syndrome. Once this is recognised, serological screening may be a useful adjunct to the diagnosis.¹⁵

The postenteritis syndrome of infancy and early childhood seems to be distinct from postinfective malabsorption or tropical sprue in adults as reviewed by Cook.¹⁶ Although in older children this syndrome may occur. What all the syndromes of infancy described show is some degree of small intestinal mucosal damage – that is, enteropathy. Folate deficiency is not, however, a feature of the postenteritis syndrome in infancy and early childhood.

POSTENTERITIS ENTEROPATHY: INFECTIVE ENTEROPATHY

Postenteritis enteropathy may result from infection continuing to cause damage. The best example of this is provided by infection with enteroadherent *E coli* of the cytotoxic variety producing small intestinal mucosal damage (Fig 1). This may occur as one variant of the intractable diarrhoea syndrome described as 'Traveller's diarrhoea with a vengeance'.^{17 18} This concerns children known to be well in the land of their birth (United Kingdom) but who develop severe diarrhoea when taken to their ancestral homeland (Indian subcontinent, etc) where they are exposed to a heavily contaminated environment. Small intestinal biopsy in these children shows an enteropathy with clear evidence of infection, for example, bacteria may be identified upon the surface of the mucosa adhering to the enterocytes on histological section (Fig 1).

A similar situation may occur in combined immunodeficiency syndromes where for example rotavirus may persist with an enteropathy. Chronic rotavirus infection is always associated with disturbed immune function.

The finding of enteropathy in a child with the post-enteritis syndrome may also be caused by a secondary or acquired infection. For example, Phillips has found astro-virus and adenovirus in the mucosa of children having a biopsy for the postenteritis syndrome who presumably have had intercurrent illnesses accounting for the virus in the abnormal mucosa.

Recently cryptosporidiosis has been recognised as an important cause of this syndrome (Fig 2).¹⁹

POSTENTERITIS ENTEROPATHY: FOOD SENSITIVE ENTEROPATHY

It is clear that some children with a postenteritis enteropathy have a food sensitive enteropathy, most often cows' milk sensitive enteropathy. The question that must arise is why does this occur or even why don't all children who develop acute gastroenteritis develop this problem?

A partial explanation may be because there is an immunodeficiency state in those who do, either locally in the small intestine or systemically.

In eight of 20 cases of cows' milk sensitive enteropathy complicating acute gastroenteritis described by Harrison *et al*²⁰ at the time of diagnosis serum immunoglobulin A concentrations were low rising to normal values with recovery.

Increased antigen entry may also play a part. There is

certainly evidence that anatomical pathways do exist for antigen entry in the biopsy specimens of children with postenteritis enteropathy.²¹ These may be shown by means of horseradish peroxidase uptake in specimens from children with postenteritis enteropathy. Thus there is morphological evidence that antigen entry can occur but what is critical is whether such entry is associated with sensitisation.

A key factor here may be the antigenicity of allergenicity of the food, usually cows' milk, fed at the time of acute gastroenteritis. There are both animal and clinical findings to suggest that allergenicity is of critical importance. The declining importance of cows' milk sensitive enteropathy in Western societies may relate to reduced antigenicity of modern feeds.

Malnutrition may play a part by interfering with the ability of the damaged mucosa to recover; however, the importance of malnutrition as a cause of enteropathy has been exaggerated in the past.²²

Such food sensitive enteropathy may overlap with an infective enteropathy as they may both coexist. Walker-Smith *et al*²³ described five children with postenteritis enteropathy who responded to a cows' milk free diet yet who also had evidence of infection at the time of biopsy.

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- 1 Huilan S, Zhen LG, Mathan MM. Etiology of acute diarrhoea among children in developing countries. *Bull World Health Organ* 1991; **69**: 549–55.
- 2 Cook SM, Glass RI, Le Baron CW. Global seasonality of rotavirus infections. *Bull World Health Organ* 1990; **68**: 171–7.
- 3 Newman G. *Infant mortality: a social problem*. London: Methuen, 1906.
- 4 Lewis J. Providers, 'consumers', the state and the delivery of health-care services in twentieth century Britain. In: Wear A, ed. *Medicine in society*. Cambridge: Cambridge University Press, 1992: 317–47.
- 5 Esrey SA, Habicht JP. Epidemiological evidence for health benefits from improved water and sanitation in developing countries. *Epidemiol Rev* 1986; **8**: 117–28.
- 6 Esrey SA, Potash JB, Roberts L, Shiff C. Effects of improved water supply and sanitation on ascariasis, diarrhoea, dracunculiasis, hookworm, infection, schistosomiasis and trachoma. *Bull World Health Organ* 1991; **9**: 609–21.
- 7 Hope EW. Observations on autumnal diarrhoea in cities. *Public Health* 1899; **12**: 661–2.
- 8 Howie PW, Forsyth JS, Ogston SA, Clark A, Florey CD. Protective effect of breast feeding against infection. *BMJ* 1990; **300**: 11–6.
- 9 Mata LJ, Kronmal RA, Garcia B, Butler W, Urrutia J, Murillo S. Breast feeding, weaning and the diarrhoeal syndrome in a Guatemalan Indian village. *Ciba Found Symp* 1976; **42**: 311–38.
- 10 Jason JM, Nieburg P, Marks JS. Mortality and infectious disease associated with infant feeding practices in developing countries. *Pediatrics* 1984; **74**: 702–7.
- 11 Weinberg RJ, Tipton G, Klish WJ, Brown MR. Effect of breast feeding on morbidity in rotavirus gastroenteritis. *Pediatrics* 1984; **74**: 250–3.
- 12 Berger R, Hadziselimovic F, Just M, Reigel F. Influence of breast milk on nosocomial rotavirus infections in infants. *Infection* 1984; **12**: 171–4.
- 13 Yolken RH, Peterson JA, Vonderfecht SL, Fouts ET, Midthun K, Newburg DS. Human milk mucin inhibits rotavirus replication and prevents experimental gastroenteritis. *J Clin Invest* 1992; **90**: 1984–91.
- 14 Thomas AG, Phillips AD, Walker-Smith JA. The value of proximal small intestinal biopsy in the differential diagnosis of chronic diarrhoea. *Arch Dis Child* 1992; **67**: 741–4.
- 15 Khoshoo V, Bhan MK, Unsworth DJ, Kumar R, Walker-Smith JA. Antireticulin antibodies: useful adjunct to histopathology in diagnosing coeliac disease, especially in a developing country. *J Pediatr Gastroenterol Nutr* 1988; **7**: 864–6.
- 16 Cook GC. Aetiology and pathogenesis of post-infective tropical malabsorption (tropical sprue). *Lancet* 1984; **i**: 721–3.
- 17 Hutchins P, Hindocha P, Phillips AD, Walker-Smith JA. Traveller's diarrhoea with a vengeance in children of UK immigrants visiting their parental homeland. *Arch Dis Child* 1982; **57**: 208–11.
- 18 Msengi AE, Phillips AD, Risdon RA, Walker-Smith JA. Traveller's diarrhoea among children returning to the UK from visits abroad. *Ann Trop Paediatr* 1988; **8**: 173–80.
- 19 Phillips AD, Thomas AG, Walker-Smith JA. Cryptosporidium, chronic diarrhoea and the proximal small intestinal mucosa. *Gut* 1992; **33**: 1057–62.
- 20 Harrison BM, Kilby A, Walker-Smith JA, France NE, Wood CBS. Cows' milk protein intolerance: a possible association with gastroenteritis, lactose intolerance and IgA deficiency. *BMJ* 1976; **1**: 1501.
- 21 Jackson D, Walker-Smith JA, Phillips AD. Macromolecular absorption by histologically normal and abnormal small intestine mucosa in childhood: an in vitro study using organ culture. *J Pediatr Gastroenterol Nutr* 1983; **2**: 235–48.
- 22 Walker-Smith JA. *Diseases of the small intestine in childhood*. 3rd ed. London: Butterworths, 1988: 433–4.
- 23 Walker-Smith JA, Harrison M, Kilby A, Phillips AD, France NE. Cows' milk sensitive enteropathy. *Arch Dis Child* 1978; **53**: 375.