

SPECIAL ARTICLE

Gastrointestinal Aspects of Malnutrition in Children

by

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Introduction

Throughout history mankind has suffered many scourges. In many parts of the world improvements in living standards, hygiene, nutrition, medical care and preventive public health programmes have made many of these infectious diseases things of the past. However, in the so-called "developing" countries, diarrhoeal diseases of infancy and childhood are still major problems which cause many millions of deaths each year (Mata, 1985).

Knowledge about the underlying causes of diarrhoeal illnesses in childhood malnutrition is essential for the planning of appropriate strategies to help overcome the problem. A tendency to think of these diseases as being "tropical" must be avoided since they were common enough, even last century, in the presently industrialized nations of Britain and Western Europe (Wharton, 1975; Gracey, 1987) and, indeed, are still serious problems in impoverished minority groups in otherwise affluent societies. The high incidence and severity of diarrhoeal diseases in young Australian Aborigines is an outstanding

example of such an anomaly (McNeilly et al, 1983; Gracey et al, 1983).

Many studies of gastrointestinal disease in malnourished children have concentrated on the patterns of infectious microorganisms which cause acute diarrhoea and significant advances have been made in this field over recent years. Evidence is available which implicates environmental factors as a significant underlying cause; this is important because of its medical, sociological, educational and even political implications, all of which are relevant to paediatricians where malnutrition and its accompanying infectious diseases, including diarrhoea, are prevalent.

One of the characteristic features of malnourished children is their proneness to infections, particularly of the respiratory and gastrointestinal systems. Apart from increased susceptibility to infection because of debility and impaired immune responses, this is related to heavy exposure to infectious agents which are associated with poverty, overcrowding and unhygienic living conditions.

Infections and Infestations

Until recently, the rate of isolations of enteric pathogens in most reported series of childhood gastroenteritis was quite low. However, these reports were mostly from temperate regions (Cramblett et al, 1971) and a wide range of recognized stool pathogens including *Escherichia coli*, salmonella, Shigella and parasites can be isolated much more readily from subjects in developing countries (Sebedo et al, 1978) or from underprivileged with malnutritions, including gastroenteritis.

Major advances in understanding infectious diarrhoeas include the discoveries that viruses, enterotoxigenic bacteria and a range of "newer" diarrhoea-producing micro-organisms can cause gastroenteritis in children.

Enterotoxigenic bacteria

Traditional thinking about enteropathogenicity needs revision. For example, doubts have been cast on the usefulness of serotyping to identify enteropathogenic *E. coli*, some of which are not serotypically pathogenic and are not invasive, yet are capable of causing net intestinal fluid and electrolyte loss and diarrhoea (Levine et al, 1978; Editorial, 1983).

Much of the information about how *E. coli* and other enteric bacteria cause diarrhoea comes from studies of intestinal fluid loss in cholera; the prime example of a toxin-induced, watery diarrhoea. Several mechanisms are involved, including production of colonization factor antigens, bacterial adherence to the intestinal mucosa and production of enterotoxins. The ability to produce enterotoxins (enterotoxigenicity) is not restricted to enterotoxigenic *E. coli* (ETEC) and *V. cholerae*; other bacteria with this capability include *Aeromonas*, *Klebsiella*, some enteropathogenic

E. coli, *Shigella dysenteriae I*, *Staphylococcus aureus*, *Clostridium perfringens*, *Clostridium difficile*, *Bacillus cereus* and *Yersinia* (Gracey, 1985). Adherence to the gastrointestinal mucosa is a major factor in determining enteric pathogenicity (Evans and Evans, 1978). Enterotoxigenic strains of *E. coli* produce a heat-labile toxin (LT), a heat-stable toxin (ST) or both.

Identification of enterotoxigenic bacteria has been hampered by the lack of simple, reliable, portable diagnostic methods and has relied on complex techniques such as cell culture, the suckling mouse assay or ligated ileal loop methods, which are usually unavailable in developing countries except in some research laboratories. This is a serious problem because there is strong evidence that ETEC are an important cause of diarrhoea in young children in developing countries (Carpenter, 1980). The use of polyvalent antisera to recognize serotypes which were commonly associated with enterotoxicity in strains from Bangladesh has recently been proposed as a relatively simple screening method for ETEC (Merson et al, 1980) but geographical variation in the association of serotypes with enterotoxin production seems to seriously limit the usefulness of this system (Berry et al, 1983). More recently, Burke et al (1987) have found that even simpler biotyping characteristics could be used to help develop selective media to increase the yield of ETEC in diagnostic laboratories. This could be useful while gene probes to identify ETEC become improved, simplified and produced in systems that are inexpensive and feasible for widespread use in developing countries (Moseley et al, 1982).

Enteroinvasive *E. coli* (EIEC) resemble *Shigella* spp. and cause similar dysenteric

clinical features with diarrhoea accompanied by blood and mucus (Silva et al, 1980). Recently, a newer form of disease producing *E. coli* has been recognized, the enteroadherent *E. coli* (EAEC). These strains do not produce recognized enterotoxins, do not belong to recognized EPEC serogroups, but adhere to HEp-2 cells cultured *in vitro* and have been associated with

diarrhoea in American travellers to Mexico (Mathewson et al, 1985). Ongoing studies of the epidemiology of *E. coli* diarrhoea in Australian Aboriginal children (unpublished) suggest that EAEC may be important in these children who have a high incidence of diarrhoeal diseases in the first few years of life.

Other "newer" causes of bacterial diarrhoea

Campylobacter spp. have become widely recognized as a major cause of acute diarrhoea, especially in children, and simple, selective procedures are available for their isolation (Skirrow, 1977; Karmali and Fleming, 1979). In our own experience of almost a thousand children with acute diarrhoea in Perth we found *Campylobacter* spp. in 7.4% (compares with 0.6% in controls) compared with *Salmonella* in 5.7%, ETEC in 1.9% and *Shigella* in 1.3% (Burke et al, 1983). The typical clinical picture of *Campylobacter* infections in children includes prodromal fever, muscle pain, headache and abdominal pain which after a few days leads to colicky pain with diarrhoea and bloody diarrhoea occurring a day or two later; the stools contain an acute inflammatory exudate and the colonic mucosa is acutely inflamed (Blaser et al, 1983).

The rate of isolation of *Campylobacter* from human faeces seems to be closely related to standards of hygiene and is much higher in developing countries than in industrialized countries (Blaser et al, 1980a and b). *Campylobacteriosis*, like salmonellosis, is a zoonotic infection and various animals including dogs, cats, poultry, cattle and sheep can be infected and involved in its transmission (Blaser et al, 1980b); several routes of transmission are possible including person-to-person, ani-

mal-to-animal, or through contaminated food, milk or water (Itoh et al, 1982; Robinson et al, 1979; Mentzing, 1982).

Aeromonas

Reports of *Aeromonas*-associated diarrhoea have since been made from many parts of the world (see Burke and Gracey, 1986, for review) including North America, Europe, Australia, India, Africa and South-East Asia, including Indonesia (Santoso et al, 1986).

Aeromonas species are widely distributed in the environment and occur in different animal species including frogs, fish, reptiles and laboratory animals. Contaminated waters are likely to be sources for human gastrointestinal infections whether they are recreational water, such as swimming pools (Millership and Chattopadhyay, 1985), lakes or estuaries (Seidler et al, 1980) or whether they are domestic water supplies (Burke et al, 1984).

Aeromonas-gastroenteritis has two age peaks: in young children (Freij, 1984) and in adults 60 years of age and over (Millership et al, 1983; Agger et al, 1985). In children there are three main clinical pictures: watery diarrhoea for several days; chronic, watery diarrhoea lasting up to 3 months; or diarrhoea with blood and mucus resembling dysentery or inflammatory bowel disease (Gracey et al, 1982). *Aeromonas*

spp. have recently been recognized as a cause of travellers diarrhoea (Gracey et al, 1984).

Plesiomonas shigelloides

Plesiomonas shigelloides can cause epidemic outbreaks of watery diarrhoea and seems to be important in India (Sanyal et al, 1975), other tropical areas, and Japan (Tsukamoto et al, 1978). The disease is probably water-borne and, although some strains are toxigenic, the pathogenesis of the infection is obscure (Sanyal et al, 1975).

Vibrio parahaemolyticus

Infections with *V. parahaemolyticus* seem to affect adults more than children and tend to occur in summer, perhaps because of infection through contaminated food, seawater or consumption of contaminated seafood (Blake et al, 1980). The disease usually causes watery diarrhoea although dysenteric symptoms, with blood and mucus in the loose stools, may occur. Important outbreaks have occurred in Japan, India and South-East Asia (Blake et al, 1980); it has also been reported from the United States (Barker, 1974).

Yersinia

Yersinia enterocolitica is usually due to *Y. enterocolitica* and most episodes occur in children less than seven years old (Kohl et al, 1976). The disease usually causes fever, vomiting, abdominal pain and diarrhoea, often with blood, mucus and an inflammatory exudate. The clinical features can resemble inflammatory bowel disease (Savage and Dunlop, 1976) or, in older patients, features similar to mesenteric adenitis (Pai et al, 1982).

Viruses

The earliest reports implicating viruses in childhood "gastroenteritis" came from

the demonstration by electron microscopy of virus-like particles in the duodenal mucosa and stools (Bishop et al, 1973, 1974). Later studies using immune electron microscopy confirmed the presence of specific antibodies after infection and immunofluorescence studies have detected specific immunoglobulin responses. Serological tests are now available for accurate and rapid identification of these viruses and to detect the humoral responses to viral infection, including enzyme linked immunosorbent (ELISA) assays.

Rotavirus gastroenteritis is predominantly a disease of under 2-year-olds with a peak incidence about 9-12 months (Brandt et al, 1983) and with most episodes occurring during winter in temperate climate. In the tropics rotavirus enteritis tends to occur throughout the year although seasonal increases have been reported in both the dry season (Hieber et al, 1978) and the wet (Blacklow and Cukor, 1981). Outbreaks in neonates also can occur throughout the year.

Rotavirus infection is transmitted by the faecal-oral route (Davidson et al, 1975) and spread can occur within families (Wenman et al, 1979; Greenwood et al, 1983). The incubation period of rotavirus infection is 2 to 3 days; this is followed by fever, then diarrhoea and vomiting which is sometimes preceded or accompanied by upper respiratory tract symptoms (Rodriguez et al, 1977). The stools are usually fluid, often quite large and are usually without blood or mucus. Diarrhoea is usually worst on the second or third day and the illness is usually self-limiting within a week or so. Because of mucosal involvement, secondary lactose intolerance is common but usually resolves within 2 to 4 weeks (Davidson et al, 1984). This form of sugar intolerance can cause chronic diarrhoea, particularly in undernourished children with a history of inter-

mittent or recurrent gastrointestinal infections, in whom lactose intolerance may last for many months (Davidson, 1986).

There are several other groups of viruses which can cause acute diarrhoea; these are not routinely sought in diagnostic laboratories and their incidence in childhood gastroenteritis is not so well documented as it is with rotavirus.

An agent which caused an outbreak of diarrhoea and vomiting in Norwalk, Ohio, in 1968 became known as the Norwalk agent (Blacklow et al, 1972). Norwalk virus is thought not to be an important cause of severe gastroenteritis but it can affect older subjects of any age. It may be relatively more important in infants and young children in developing countries (Kapikian

et al, 1982). The disease is milder and shorter than rotavirus gastroenteritis.

Morphologically typical adenoviruses have been isolated by many investigators from faecal specimens of children with acute diarrhoea and appear to be emerging as the next most common viral agents, after rotavirus, in childhood gastroenteritis (Brandt et al, 1983; Uhnoo et al, 1984).

Faecal coronaviruses have been reported from patients with diarrhoea, but their significance is unknown although experience with a fatal infection accompanied by diarrhoea in a 15-month old child has been published (Rettig and Altshuler, 1985).

Astroviruses and caliciviruses may also be involved in episodes of acute gastroenteritis.

The intestinal bacterial flora

The upper small intestine is significantly contaminated by large numbers of bacteria in children with malnutrition. The earliest published reports were from malnourished young Australian Aborigines (Gracey and Stone, 1972), from Guatemalan children studied at the Institute of Nutrition of Central America and Panama (Mata et al, 1972) and from collaborative studies done in Indonesia (Gracey et al, 1973). These reports were followed by others from Africa supporting bacterial contamination of the upper gut as an important aspect of childhood malnutrition (Heyworth and Brown, 1975; Rowland et al, 1977). All of these studies suffer from the disadvantage of lacking strictly comparable, local control material from healthy children which, naturally, is extremely difficult to obtain since per-oral intestinal intubation is involved. It is uncertain, therefore, whether the upper intestinal microflora in malnourished children is comparable to that occurs in Western countries where living condi-

tions, in general, are more hygienic than in developing countries. Mehta et al (1985) have helped to overcome this problem with a study from India which showed 11 out of 20 normally nourished children had sterile jejunal contents, three had bacterial counts of less than 10^4 /ml and six (30%) had higher counts, in contrast to a 75% yield (30/40) in malnourished children with or without chronic diarrhoea.

Consequences of intestinal bacterial contamination

Bacterial overgrowth of the proximal gut produces a range of clinical effects including steatorrhoea (fat malabsorption), carbohydrate malabsorption, hypoproteinaemia, vitamin B₁₂ deficiency and associated macrocytic anaemia and iron deficiency. These effects are related to the bacterial degradation of bile salts affecting micellar solubilization of fat, damage to the function of mucosal enterocytes and bacterial binding of vitamin B₁₂ (Gracey,

1979; King and Toskes, 1979; Simon and Gorbach, 1986).

In malnutrition these and other mechanisms may operate, especially with recurrent and chronic gastrointestinal infections and infestations damaging the intestinal mucosa. Toxigenic bacteria, particularly

The gastrointestinal mucosa

In apparently healthy adults living in the tropics the small intestinal villi are shorter and wider than in Western subjects; the enterocytes are more irregular and there is an increase in the numbers of inflammatory cells in the lamina propria (Sprinz, 1962). In malnourished children the mucosal abnormalities are quite marked with severe histological alterations in the proximal small intestinal epithelium, including thinning of the gut wall, marked flattening and broadening of the villi, extensive inflammatory infiltration of the lamina propria and transformation of the shape of the enterocytes from columnar to cuboidal or squamous (Schneider and Viteri, 1972). Such changes have been widely reported and are accompanied by very extensive ultrastructural damage to the mucosal epithelial cells (Brunser et al, 1976). This is probably related to the development of 'tropical enteropathy' (Tomkins, 1981) or what the Chileans call 'chronic environmental enteropathy' (Brunser et al, 1984) and, perhaps, tropical sprue in later life (Cook, 1984).

The gastric mucosa is also damaged and gastric acid secretion markedly reduced in response to stimulation by pentagastrin (Gracey et al, 1977). Secretion of hydrochloric acid is one of the factors which normally controls the upper intestinal microflora and loss of this mechanism in malnutrition may contribute to the heavy bacterial populations found in the upper gut.

species of *E. coli*, are likely to be specially important because of their prevalence in the gastrointestinal tract in malnourished children and their capacity to produce toxins which interfere with the intestinal absorption of fluids and electrolytes (Thelen et al, 1978).

Intestinal digestion and absorption

The brush border surface of the enterocytes normally has an important digestive function because of the localization of digestive enzymes, including disaccharidases, in this part of the cell (Miller and Crane, 1961). The extensive histological damage which occurs in protein-energy malnutrition (PEM) causes secondary depression of the activity of brush border enzymes and lactose intolerance occurs in about a quarter of patients (Bowie et al, 1965; Wharton et al, 1968). In many countries where malnutrition remains a major problem, e.g. in South East Asia, late-onset hypolactasia is very prevalent in certain ethnic groups (Chung and McGill, 1968) and this additional factor has to be considered when planning nutritional management.

Intestinal absorption, as well as digestion, may be impaired in malnutrition. This may manifest clinically, for example, as a temporary inability to absorb all sugars including profuse diarrhoea, severe dehydration and metabolic acidosis and can be life-threatening (Gracey and Burke, 1973).

The clinical features of this disorder are similar to those of disaccharide intolerance but do not respond to removal of disaccharides from the diet if monosaccharides such as glucose, fructose or galactose, remain in the feeding formula. These patients are often young and severely malnourished and have very profuse, watery diarrhoea. They

require very careful clinical and dietary management. A carbohydrate-free feeding formula can be a useful and well tolerated source of dietary energy (calories) for these patients which permits the gradual and carefully supervised introduction of sugars into the formula. It can also be used as an additional dietary energy source in patients on intravenous therapy who are unable to tolerate sugars given by mouth.

Malabsorption of other nutrients, such as fat, also occurs in malnutrition. As with most of the clinical features of PEM, including its strong association with diarrhoeal diseases and malabsorption, many interrelated factors can be involved (Viteri and Schneider, 1974); for example, altered bile salt metabolism, impaired hepatic and pancreatic function and, in severe malnutrition, fatty infiltration of the liver (Waterlow, 1975).

The combined effects of reduced intesti-

The environment

The gastrointestinal tract is constantly exposed to external influences, including diet and microorganisms, which have considerable potential to affect nutritional status. Despite this and the close connections between diarrhoeal diseases and unhygienic living conditions, there are few quantitative studies which link the two.

Heavy faecal pollution of water used for domestic purposes has been found in association with a high rate of isolation of faecal bacteria and enteric pathogens in the oro-pharyngeal secretions of children in a crowded tropical city (Gracey et al, 1973; Gracey et al, 1979a); this microbiological abnormality has been proposed as a relatively simple indicator or significant environmental pollution (Gracey et al, 1979b). Contamination of foodstuffs and water is an important source of diarrhoea in infants

and young children in Africa (Rowland et al, 1978; Tomkins et al, 1978; Rowland 1982; Rowland 1985). We have made similar observations (unpublished) in Aboriginal communities in remote parts of Western Australia where coliforms, a recognized index of water quality, were found frequently in water stored in contaminated metal containers and where food and drink prepared and stored unhygienically was often contaminated by gram positive microorganisms and yeasts. Such conditions are consistent with the high prevalence of gastrointestinal disease in these communities and the ready isolation of pathogenic microorganisms from gastrointestinal specimens from these places. In relation to prevention of diarrhoeal disease, this is crucial since programmes which concentrate on nutritional problems alone and

ignore the environment as a source of repeated infections are bound to have little success.

The common background of poverty, ignorance, overcrowding, undernutrition and poor hygiene contributes very significantly to acute diarrhoeal diseases of children in developing countries. Improvements in personal and community living standards are pre-requisites to the ultimate control or eradication of these diseases.

The World Health Organization has recognized the seriousness of the diarrhoeal diseases problem through the development of its Control of Diarrhoeal Diseases Pro-

gramme which is designed to overcome this challenge. This includes improvements in drug and dietetic treatment of diarrhoea, better nutrition of mothers and children, improvements to water supplies, sanitation and food hygiene, health education, epidemiological surveillance and control of outbreaks of disease and immunization programmes. Many of these can be implemented with currently available knowledge, but an increased and sustained effort is needed to help control one of the most difficult and challenging problems which faces paediatricians in many parts of the world.

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