Acute Diarrhoea in Childhood

Ciba Foundation Symposium 42 (new series)

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Acute Diarrhoea in Childhood
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Editors: KATHERINE ELLIOTT (Organizer) and JULIE KNIGHT
During 1975, five hundred million episodes of diarrhoea were likely to occur among the babies and small children of Asia, Africa and Latin America; and the disease would kill between five and eighteen million of them. Despite the tremendous advances made in medicine over the last few decades, gastroenteritis remains largely responsible for the high death rate in infancy and early childhood in many tropical countries and poorer communities and it is still a danger within prosperous societies.

Professor Otto Wolff and Dr John Harries of the Institute of Child Health in London suggested that the Ciba Foundation should bring together work on childhood diarrhoea of bacterial origin with the new and fast developing work on diarrhoea due to viral infections in infants and young children. Their idea gave rise to the symposium recorded in this book. We received valuable help in the planning also from Dr Geoffrey Sharp, Dr T. H. Flewett, Dr W. E. van Heyningen and Professor Ralph Hendrickse.

Many factors contribute to acute diarrhoea in early childhood, and it was not possible to explore in detail all of them at the symposium. Protozoal causes were deliberately omitted as formal topics, but are mentioned as contributory pathogens with interactions which require further research. Initially the symposium concentrates on identifying bacterial and viral causative agents, including the analysis of the mode of action of enterotoxins and the transmission of enterotoxin production by plasmids in Escherichia coli. The complex pathogenesis of overt diarrhoea and the implications for its clinical management are discussed, considerable stress being laid on protection by colostrum and breast milk.

Viral gastroenteritis affects the young of all mammals. Before successful preventive therapy can be developed, more research is needed into the transport defects and immunological mechanisms involved.
The symposium ends with accounts of diarrhoea among children in the developing world where deprivation complicates the picture. Poor nutrition, unsafe water supplies and frequent exposure to intercurrent infections combine with understandable ignorance to create conditions in which gastroenteritis becomes a constant extra and often final hazard. The disease induces a state of fluid electrolyte malnutrition. If simple guidelines are followed which match fluid intake to thirst and stool output, oral rehydration using a glucose-electrolyte solution is a simple, cheap and effective remedy. Professional training is not required for this treatment of diarrhoeal disease, and it will save many young lives if it can become common.

But further research is needed at every level. Diarrhoea must be looked at both in the micro-environment of the host-pathogen interaction and in the macro-environment of man in his society. And workers at all levels should be constantly alert to potentially useful exchanges of ideas in order that, as Dr Jon Rohde urges at the end of the symposium, science may be taken to where the diarrhoea is.

Katherine Elliott
The problem of bacterial diarrhoea

J. T. HARRIES
Institute of Child Health, and The Hospital for Sick Children, London

Abstract

The reported incidence of 'pathogenic' bacteria, as judged by serotype, in the stools of children with acute diarrhoea has varied from 4 to 33% over the last twenty years. Techniques such as tissue culture provide a means for detecting enterotoxin-producing strains of bacteria, strains which often do not possess 'pathogenic' serotypes. 'Pathogenicity' requires redefinition, and the aetiological importance of bacteria in diarrhoea is probably considerably greater than previous reports have indicated.

Colonization of the bowel by a pathogen will result in structural and/or mucosal abnormalities, and will depend on a series of complex interactions between the external environment, the pathogen, and the host and its resident bacterial flora. Enteropathogenic bacteria may be broadly classified as (i) invasive (e.g. Shigella, Salmonella and some Escherichia coli) which predominantly affect the distal bowel, or (ii) non-invasive (e.g. Vibrio cholerae and E. coli) which affect the proximal bowel. V. cholerae and E. coli elaborate heat-labile enterotoxins which activate adenylate cyclase and induce small intestinal secretion; the secretory effects of heat-stable E. coli and heat-labile Shigella dysenteriae enterotoxins are not accompanied by cyclase activation.

The two major complications of acute diarrhoea are (i) hypernatraemic dehydration with its attendant neurological, renal and vascular lesions, and (ii) protracted diarrhoea which may lead to severe malnutrition. Deconjugation of bile salts and colonization of the small bowel with toxigenic strains of E. coli may be important in the pathophysiology of the protracted diarrhoea syndrome.

The control of bacterial diarrhoea requires a coordinated political, educational, social, public health and scientific attack. Bacterial diarrhoea is a major health problem throughout the world, and carries an appreciable morbidity and mortality. This is particularly the case during infancy, and in those developing parts of the world where malnutrition is common. This paper is concerned mainly with acute bacterial diarrhoea, and reviews the problem as a whole.

INCIDENCE, DISTRIBUTION AND PATHOGENIC SPECIES

The reported incidence of 'pathogenic' bacteria cultured from the stools of
children (mainly less than two years old) with acute diarrhoea has varied from 4 to 33% over the last 20 years (Cramblett et al. 1971), the commonest organisms being 'enteropathogenic' strains of *Escherichia coli* (EPEC), *Salmonella* and *Shigella*. Stools were not cultured from control children in all of these studies, and the true pathogenicity of the isolated bacteria is therefore not always clear. It is now clear that enterotoxin-producing strains of *E. coli* can cause diarrhoea in both adults and children, and also that the somatic serotypes of these strains are often not the recognized EPEC (Gorbach & Khurana 1972; Gorbach et al. 1975; Sack et al. 1975). The term 'enteropathogenic' as applied to serotypes of *E. coli* requires redefinition. The detection of enterotoxin-producing strains of bacteria by the use of techniques such as the rabbit ligated loop and tissue culture will probably show that the aetiological importance of bacteria in diarrhoeal illness in children is considerably greater than previous reports have indicated.

Table 1 shows the geographical distribution of the established bacterial pathogens in man, and the age groups mainly affected. Mortality and morbidity is much greater under the age of two years than in older children, and the commonest pathogens during this critical period of physical and intellectual development are *E. coli, Salmonella* and *Shigella*. Curiously, cholera is rare in infants under the age of one year (Mosley et al. 1968). Toxigenic strains of staphylococci are ubiquitous and most foods cannot fail to become contaminated with small numbers of viable organisms. They produce enterotoxins in food and disease results from ingestion of preformed toxin; the majority of outbreaks of food poisoning caused by staphylococci are due to the coagulase-positive species. *Vibrio parahaemolyticus* differs from *V. cholerae* in being a marine organism, and has been found mainly in Japan where it has been a major cause of outbreaks of food poisoning (Zen-Yoji 1968); this is probably related to the Japanese custom of eating uncooked fish. Other vibrios such as

<table>
<thead>
<tr>
<th>Bacterial species</th>
<th>Distribution</th>
<th>Age group mainly affected</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>Global</td>
<td>0–5 years</td>
</tr>
<tr>
<td>Salmonellae</td>
<td>Global</td>
<td>All</td>
</tr>
<tr>
<td>Shigellae</td>
<td>Global</td>
<td>0–8 years</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>Asia and contiguous areas</td>
<td>All</td>
</tr>
<tr>
<td><em>Vibrio parahaemolyticus</em></td>
<td>Japan</td>
<td>Adults</td>
</tr>
<tr>
<td><em>Clostridium perfringens</em></td>
<td>Global</td>
<td>All</td>
</tr>
<tr>
<td>Staphylococci</td>
<td>Industrialized nations</td>
<td>All</td>
</tr>
</tbody>
</table>
V. fetus, or related vibrios, have been implicated as the cause of infantile diarrhoea (Mandel & Ellison 1963). Clostridium perfringens is one of the commonest causes of food-borne diarrhoea (Center for Disease Control 1970), and can produce a fatal enteritis known as ‘Darmbrand’ in Germany (Jeckeln 1947) and ‘pig-bel’ in the highlands of New Guinea (Murrell et al. 1966). It is present in faeces, water and soil and can contaminate most commercially available meat and poultry. Other bacterial species which have been implicated as occasionally causing diarrhoea are Pseudomonas aeruginosa, Aeromonas hydrophila, Edwardsiella tarda, Yersinia enterocolitica, Bacillus cereus and Bacillus subtilis (Grady & Keusch 1971a). The role of these species in the causation of diarrhoea, however, is far from clear and further carefully controlled studies are required.

DISEASE DETERMINANTS

Colonization of the bowel by sufficient numbers of pathogenic bacteria results in disease. Colonization will depend on a complex series of interactions between the external environment, the pathogen, and the host and its resident bacterial flora. Knowledge on many aspects of these interactions is fragmentary and a clearer understanding is of fundamental importance for the control of diarrhoeal disease.

The external environment

The most urgent and important factors which require attack lie in the environment. At the 5th Caribbean Health Ministers Conference in 1973 a strategy and plan of action to combat gastroenteritis and malnutrition in children under two years of age was formulated (1975). This is an important document and should serve as a model for other parts of the developing world. The plan includes improvement of environmental health services (e.g. safe water supplies, sewage disposal, and solid waste disposal), the development of infant welfare clinics, campaigns to encourage breast-feeding, family planning advice, improved management and follow-up of gastroenteritis and malnutrition, health and nutrition education of the public, and economic and agricultural measures. Malnutrition is probably the single most important predisposing factor to the development of bacterial diarrhoea.
Interactions between the host and bacteria

The ecology of the gut flora reflects intricate relationships between the host and bacteria, and is of fundamental importance in determining bacterially induced disease. Before considering mechanisms available to the host for the control of the bacterial flora of its alimentary tract, I shall review the available information on the flora of normal subjects.

Gastrointestinal flora in normal subjects There is no information on the bacterial flora along the whole gastrointestinal tract of the normal child. In normal adults the same bacterial species are found throughout the gastrointestinal tract, but the relative numbers show marked variation according to the sampling site (Williams & Drasar 1972). In the fasting state the stomach is virtually sterile but immediately after a meal counts of up to $10^5$/ml (streptococci, enterobacteria, bacteroides and bifidobacteria from the mouth and meal) are found; as gastric pH falls bacterial counts fall, and relatively few are grown below pH 3. Streptococci, lactobacilli, bifidobacteria and occasional bacteroides ($10^3$–$10^4$/ml) occur in the fasting proximal small gut, whilst counts of $10^5$–$10^7$/ml are seen in the distal ileum; these bacteria are ‘transients’ from the mouth. In contrast to the small gut, 99% of bacteria in the colon and faeces are anaerobes (predominantly bacteroides and bifidobacteria) in counts of $10^{10}$–$10^{14}$/g. The dominant aerobes in faeces are enterobacteria (mainly E. coli), enterococci (e.g. Streptococcus faecalis) and lactobacilli. Many favourable interactions occur between the resident bacterial flora of the alimentary tract and are important in maintaining the normal ecology (Bryant 1972); e.g. (i) certain bacteria such as Bacteroides ruminicola produce branched-chain organic acids which are essential for the growth of other bacteria, (ii) lactate-fermenting bacteria probably derive lactate from other bacteria, and (iii) $H_2$ and $CO_2$ produced by some bacteria are necessary for the growth of others.

Studies on the faecal flora of breast-fed babies (Bullen & Willis 1971) have shown a relative and absolute preponderance of bifidobacteria over E. coli/coliforms, whereas the reverse is the case in bottle-fed babies. Faeces from breast-fed babies never yielded bacteria other than bifidobacteria, bacteria of the E. coli/coliform complex and strains of anaerobic streptococci; faeces from bottle-fed babies, however, commonly contain clostridia, bacteroides and proteus species, and Pseudomonas aeruginosa. During weaning the flora becomes similar to that of the adult (Mata et al. 1972). The predominant bifidobacteria may play a contributory role in the low frequency of Shigella and other enteropathogens during breast-feeding (Mata et al. 1972), and form a good example of bacterial interactions favourable to the host.
THE PROBLEM OF BACTERIAL DIARRHOEA

TABLE 2
Mechanisms available to the host for the control of the bacterial flora of its alimentary tract

<table>
<thead>
<tr>
<th>Gastric juice:</th>
<th>[H⁺]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small gut motility</td>
<td>Inhibitory substance</td>
</tr>
<tr>
<td>Resident bacterial flora:</td>
<td>Substrate competition</td>
</tr>
<tr>
<td></td>
<td>Maintenance of [H⁺] and redox potential</td>
</tr>
<tr>
<td></td>
<td>Production of short-chain organic acids</td>
</tr>
<tr>
<td></td>
<td>Synthesis of colicins</td>
</tr>
<tr>
<td></td>
<td>Inhibition of Shigella</td>
</tr>
<tr>
<td>Immune systems</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Regulation of cell turnover and brush-border enzymes</td>
</tr>
<tr>
<td>Others:</td>
<td>Production of lysozyme by Paneth cells</td>
</tr>
<tr>
<td></td>
<td>Synthesis and interbacterial transfer of plasmids</td>
</tr>
</tbody>
</table>

Table 2 lists some of the mechanisms available to the host for the control of its gut flora.

_Gastric juice_ The protective role of the intact stomach in bacterial enteritis is supported by abundant evidence of acid sensitivity among pathogens; also salmonellosis is commoner in post-gastrectomy cases (Waddell & Kunz 1956), and patients with hypochlorhydria are more likely to get cholera (Hurst 1934; Sack et al. 1970). An unidentified inhibitory substance may also contribute to the stomach's protective influence (Smith 1966).

_Small gut motility_ Peristalsis is probably the most important factor in maintaining the relative sterility of the small intestine. Inhibitory studies using opiates, ganglion blockers, antiperistaltic pouches and ligation provide good evidence on how reduced motility provides favourable conditions for pathogens to colonize the small bowel (Grady & Keusch 1971b); this may explain why opium addicts are said to be more susceptible to severe attacks of cholera (Gorbach 1975). Impaired motility may also result in overgrowth of the small intestine by bacteria not normally considered pathogenic and, as a result of substrate metabolism, such as bile salt degradation (Guiraldes et al. 1975), may produce diarrhoea.

_Resident flora_ The resident bacterial flora possesses a number of mechanisms which protect the host from pathogens, and maintain the normal ecosystem (Grady & Keusch 1971b; Bryant 1972); for example (i) substrate competition, (ii) maintenance of [H⁺] and redox potential, which discriminate against invading pathogens, (iii) the production of short-chain organic acids which have
bactericidal properties in protonated form, (iv) synthesis of colicins which are bactericidal to certain strains of *E. coli*, and (v) growth of *Shigella* is inhibited by indigenous flora of the mouse intestine.

**Immune systems** The precise role of immune mechanisms in the control of the gut flora has not been clearly defined. IgA levels are high in intestinal secretions, suggesting that secretory IgA may be of importance; however, in patients with selective IgA deficiency the bacterial flora of the small intestine and faeces is normal (Brown *et al.* 1972). In contrast, patients with hypogammaglobulinaemia have moderate to excessive numbers of anaerobic bacteria in the small intestine (Brown *et al.* 1972). The role of immunodeficiency, whether primary or acquired, as a predisposing factor in acute bacterial diarrhoea is not at present clear.

Both *V. cholerae* and shigellae stimulate the production of serum bactericidal and agglutinating antibodies, but parenteral immunization with killed bacteria confers only short-term protection (Mosley *et al.* 1970; Higgins *et al.* 1955). The relative importance of systemic and local immunity to host resistance is discussed in detail elsewhere (see Pierce, pp. 129–143 and McNeish, pp. 181–190).

**Diet** A high-carbohydrate diet increases the relative numbers of bifidobacteria, whilst a high-fat diet favours bacteroides (Hoffmann 1964). People eating a mixed 'western' diet have more bacteroides and fewer aerobes than those eating the native largely vegetarian diet in Uganda, South India or Japan (Hill *et al.* 1971). *Sarcina ventriculi* is virtually confined to vegetarians in whom faecal counts may reach $10^8/g$ (Crowther 1971). The significance of these observations in relation to diarrhoeal illness is not known.

Breast-fed babies are much less likely to develop enteritis than bottle-fed babies (Gerrard 1974), and the present decline of breast-feeding throughout the world is particularly disturbing. The mechanism(s) of the protection provided by breast-feeding are probably multifactorial, and include reduced risks of contamination, immunoglobulins (Gerrard 1974) and iron-binding proteins (Bullen *et al.* 1972; Bullen, this volume, pp. 149-162) in colostrum and milk, and the preponderance of bifidobacteria in association with a low pH in the faeces (Bullen & Willis 1971; Bullen, this volume, pp. 149–162).

**Other interactions** Bacteria may play a role in regulating turnover rates of epithelial cells, and in influencing brush-border enzyme activity (Savage 1972). The lysozyme of the succus entericus is, at least partly, synthesized in the Paneth cells of the crypts and probably contributes to intestinal defence mechanisms
Plasmids are non-chromosomal genetic elements of certain bacteria which can be transferred from one bacterial strain to another by sexual conjugation. They have an important regulatory role in the biosynthesis of a wide variety of bacterial products that play a part in the survival of bacteria, and in their interactions with their host and other bacteria. Of particular importance is the demonstration that the synthesis of both heat-stable and heat-labile *E. coli* enterotoxins is under plasmid control, and the possibility that toxin pathogenicity may be a transferable factor (Gyles 1972).

**PATHOPHYSIOLOGICAL MECHANISMS**

Enteropathogens may be broadly classified as invasive or non-invasive. Invasive organisms (i.e. *Salmonella*, *Shigella*, and certain strains of *E. coli*) penetrate the mucosa of the distal small intestine and colon to produce morphological abnormalities and dysentery; studies on *Salmonella* and *Shigella* diarrhoea in the rhesus monkey have shown the jejunal mucosa to be intact, but in a secretory state with respect to the transport of fluid and electrolytes (Rout et al. 1974; Rout et al. 1975). Thus, dysentery results from mucosal disruption, and diarrhoea from jejunal secretion superimposed on the absorptive defect in the distal bowel. Except for *Sh. dysenteriae* (Keusch et al. 1972) invasive pathogens are not known to elaborate enterotoxins.

The non-invasive organisms elaborate heat-labile (*V. cholerae* and *E. coli*) and heat-stable (*E. coli*) enterotoxins in the small bowel, and induce secretion without affecting mucosal structure. The transport defect is confined to the small bowel and diarrhoea results from the normal absorptive capacity of the colon being overwhelmed. The secretory effects of the heat-labile enterotoxins of *V. cholerae* and *E. coli* are mediated by activation of the adenylate cyclase system, and these molecular interactions are considered in detail elsewhere (see van Heyningen et al., pp. 73–82; Flores & Sharp, pp. 89–103; Field, pp. 109–122).

**COMPLICATIONS**

The two most important complications of acute diarrhoea are (a) hypernatraemic dehydration, and (b) protracted diarrhoea.

**Hypernatraemic dehydration**

Hypernatraemic dehydration (i.e. serum sodium > 150 mequiv./l) is the most important complication during the acute phase with a reported incidence of
10 to 63% and a mortality rate of 4 to 20% (Ironside et al. 1970). Neurological symptoms such as irritability, convulsions, mono- or diplegia, and coma may accompany the hypernatraemia. Before rehydration, convulsions occur in 3 to 6% of infants, and in 6 to 30% during rehydration (Ironside et al. 1970). The incidence of permanent neurological sequelae may be as high as 16% (Houston 1970); the severity of the acute clinical and biochemical abnormalities is of limited value in predicting permanent neurological sequelae. Other biochemical abnormalities which accompany the hypernatraemia include uraemia, hypocalcaemia, hyperglycaemia, metabolic acidosis and hypokalaemia. Despite the high serum sodium concentration, total body sodium may be severely depleted. Hypernatraemic dehydration is more commonly seen in communities where infants are fed with feeds containing high solute concentrations (Chambers & Steel 1975), particularly if the feeds are continued in an undiluted form after the onset of symptoms. Peripheral gangrene may also complicate hypernatraemic dehydration, and may be due to disseminated intravascular coagulation (Comay & Karabus 1975). Renal vein thrombosis and medullary necrosis are also rare complications.

*Protracted diarrhoea*

In most infants symptoms resolve over the course of a few days, but in a small proportion diarrhoea persists and becomes protracted (more than four watery stools per day for longer than two weeks). The relative aetiological importance of bacterial and viral pathogens in the development of this syndrome is not known. Persistence of diarrhoea may be due to intolerance to disaccharides and/or monosaccharides, cow's milk protein (Harrison 1974), and possibly gluten; in a proportion of infants, however, the pathophysiological mechanisms responsible for the persistent diarrhoea are not clear. Colonization of the small bowel with a variety of organisms, including *E. coli* and anaerobes, is common (Gracey & Stone 1972; Challacombe et al. 1974; Schneider & Viteri 1974; Heyworth & Brown 1975), and deconjugation of bile salts has been demonstrated (Schneider & Viteri 1974). In one infant a heat-labile enterotoxin-producing strain of *E. coli* has been isolated (H. Holzel, personal communication) from small intestinal juice. We have shown that in the rat *in vivo* the unconjugated dihydroxy bile acid deoxycholate inhibits small intestinal transport of water, electrolytes and glucose, inhibits the transmural potential difference, inactivates mucosal Na⁺, K⁺-ATPase, and at high concentrations produces structural abnormalities (Harries & Sladen 1972; Guiraldes et al. 1975). Thus, toxigenic strains of *E. coli*, deoxycholate, and possibly other products of bacterial metabolism may be of pathophysiological importance in the pro-
TRACTED DIARRHOEA SYNDROME. Protracted diarrhoea is much more likely to complicate acute enteritis in infants under the age of six months, an age when malnutrition may have permanent effects on the physical and intellectual development of the child.

MANAGEMENT

General

The single most important factor in management is the correction of the fluid and electrolyte imbalance. In mild cases small-volume, frequent, diluted milk feeds are often all that is needed. In more severe cases one of the electrolyte solutions shown in Table 3 should be used; the inclusion of glucose in such solutions has been an important development in the treatment of cholera, and this may also be the case in infantile diarrhoea due to *E. coli*. The fluid requirement for infants up to the age of six months is 150 ml/kg per 24 hours but if there are early signs of dehydration, this should be increased to 175-200 ml/kg per 24 hours. Requirements are given as frequent (every 1–2 hours) small-volume (100 ml) feeds. Parents must be carefully instructed and supervised, particularly if there is any doubt of their capabilities. After 24–48 hours of clear fluids, diluted (quarter-strength) milk feeds can usually be reintroduced, and concentrated to full strength over the subsequent two to three days. The need for intravenous fluids should be carefully assessed if the infant’s condition has deteriorated or failed to improve after 24 hours of oral fluids.

There is no good evidence that antibiotics or anticholinergic agents reduce mortality or morbidity. By slowing the transit of intestinal contents and inhibiting the growth of resident bacterial flora such agents may facilitate the proliferation of pathogens and exacerbate disease, as well as prolonging faecal

**TABLE 3**

Recommended oral solutions in acute enteritis

<table>
<thead>
<tr>
<th>Solution</th>
<th>Sodium</th>
<th>Chloride</th>
<th>Potassium (mmol/litre)</th>
<th>Bicarbonate</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>80</td>
<td>70</td>
<td>18</td>
<td>28</td>
<td>100</td>
</tr>
<tr>
<td>Half-strength Darrow’s solution</td>
<td>60</td>
<td>52</td>
<td>18</td>
<td>25 (lactate)</td>
<td>–</td>
</tr>
<tr>
<td>Electrosol solution*</td>
<td>46</td>
<td>44</td>
<td>17</td>
<td>19</td>
<td>–</td>
</tr>
</tbody>
</table>

* See Editorial (1975).

* Electrosol tablets are flavoured with orange and are prescribable; eight tablets dissolved in one litre give the ionic concentrations shown above.
excretion of the pathogen after the acute illness; for example, antibiotics prolong the faecal excretion of Salmonella, thereby increasing the risk of cross-infection (Christie 1971). Severe relapse of disease has been reported in one asymptomatic carrier after treatment with ampicillin (Rosenthal 1969). Until the results of carefully controlled studies are available, antibiotics should only be considered when infection is due to an invasive pathogen (e.g. Shigella) and there is frank blood and mucus in the stools, particularly if there is a suspicion of extra-intestinal spread of the organism.

Hypernatraemic dehydration

The neurological damage results from bulk fluid shifts between the hyper-osmotic intravascular space and the brain, and is particularly likely to occur if the hypernatraemia is corrected too rapidly. If present, peripheral circulatory failure is corrected with plasma or normal saline (20 ml/kg over 60 min). Although there is general agreement that correction of the hypernatraemia with intravenous fluids should be gradual (i.e. over 36–72 hours), opinion on the composition of the fluid is varied. We have found 0.18% saline in 4.3% dextrose given at a rate of 150 ml/kg of admission weight per 24 hours to give satisfactory results in practice. Metabolic acidosis should be corrected, and potassium administered as soon as an adequate urinary output is established (usually within 10 hours of starting intravenous fluids); these measures are often associated with a return of serum calcium levels to normal, obviating the need to administer calcium. Persistent oliguria or anuria may reflect renal failure and, in these circumstances, peritoneal dialysis may be indicated. Meningitis should be excluded by lumbar puncture if neurological symptoms appear.

Protracted diarrhoea

After investigation, initial management involves the withdrawal of potentially offending dietary components such as disaccharides and cow's milk protein, by using one of the many dietary regimes that are available (Francis 1975). Dietary manipulations, however, are sometimes unsuccessful, and intravenous feeding may be life-saving (Harries 1971). In those infants who respond to dietary treatment, reintroduction of a normal diet is usually possible after two to three months, though lactose intolerance can persist for considerably longer.

THE FUTURE OF BACTERIAL DIARRHOEA

The control of bacterial diarrhoea necessitates a cooperative and systematic
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approach requiring close political, educational, social, public health and scientific collaboration. The strategy and plan of action proposed in the 5th Caribbean Health Ministers Conference in 1973 (1975) should serve as a working model for the developing parts of the world. Improvements in sanitation and nutrition in children, and propaganda to encourage breastfeeding, are urgent priorities. Live, attenuated oral vaccines hold promise but have not yet been sufficiently developed to have any major impact on the problem. The world-wide indiscriminate use of antibiotics and anticholinergic agents is not only costly, but may exacerbate diarrhoeal disease, and also encourage the emergence of resistant pathogenic strains; this is primarily a problem of medical education.

The considerable progress that has been made in recent years in our understanding of bacterial and toxin cell-binding processes, the purification of cholera toxin, and toxin–adenylate cyclase interactions, has provided an impetus and added motivation to the elucidation of the molecular events which mediate 'pathogenicity' and lead to diarrhoea. There remain, however, large areas of ignorance which need to be aggressively pursued before the jig-saw puzzle is solved. These include the complex host–pathogen interactions which determine whether a pathogen becomes established in the alimentary tract, the purification and characterization of enterotoxins, the mechanism of bacterial and toxin binding to cell surfaces, immunological studies and the development of vaccines, the mechanisms which determine invasiveness, plasmids and their regulatory functions in bacterial metabolism, and the transport abnormalities which follow adenylate cyclase activation. Solving the jig-saw puzzle is fundamental to solving the major and world-wide problem of bacterial diarrhoea in childhood.

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Discussion

Smith: Could I raise the question of the diagnosis of bacterial infections, particularly of *E. coli* diarrhoea? You mentioned reported incidences over the past 20 years as ranging from 4% to 33%, with *E. coli* being among the commonest organisms found. I wonder what such estimates are really worth. I am not happy that one can diagnose *E. coli* diarrhoea in any species of animal, certainly in babies, just by determining the serotypes of *E. coli* in their faeces. Some of the serotypes that people now consider to be enteropathogenic are non-toxigenic if the rabbit ileal loop is used as a test.

Following on from that is the question of what is meant by 'enteropathogenic'. It surely means more than enterotoxigenic. Simply finding *E. coli* in the faeces which will dilate a rabbit ileal loop doesn’t mean that it is enteropathogenic, because for that a strain has to be able to proliferate in the small intestine as well as to produce an enterotoxin.

A related point is the method used for identifying enterotoxin—for example, the ligated rabbit loop, which has had a rather chequered career, and the effects on tissue culture cells. How valid are these methods? We know that some enteropathogenic animal strains of *E. coli* dilate the ligated intestine of the species in which they produce diarrhoea but do not dilate the intestine of a rabbit. One is interested, in the baby strains, not in whether they dilate rabbit intestine but in whether they dilate baby intestine.

Harries: On that point, you have been working on the ligated loop preparation for many years, and I am interested in your comments on it. What in your view is the usefulness of the rabbit ligated loop?

Smith: In domestic animals we are in the fortunate position that we can test strains of *E. coli* in ligated loops of the same species of animal as that from which they were isolated. In man you usually have to use the rabbit loop. It is a valuable test but it’s not 100% by a long way. Some *E. coli* enteropathogenic for piglets, for example, produce an enterotoxin which dilates piglet intestinal loops very powerfully but has no effect on the rabbit loop. Unfortunately, too, with the rabbit loop, one is using the intestine of a species which as far as I know does not suffer from *E. coli* diarrhoea.
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Pierce: With human strains of E. coli we find almost 100% correlation between positivity of LT-producing strains in the rabbit gut loop and their detection by Y-1 mouse adrenal tumour cells or Chinese hamster ovary cells in tissue culture. This applies to challenge of the rabbit gut loop with either toxin in culture filtrates or viable organisms. Although it is tedious, and not necessarily the ideal assay procedure, the rabbit gut loop assay is extremely useful.

Hendrickse: I would like to make a few more general points. I worked in Africa for many years and a major clinical problem there is to decide just what is meant when a parent complains that a child has ‘diarrhoea’. The definition of diarrhoea is so vague, and the complaint so prevalent, that clinical studies, in particular therapeutic trials, on unspecified diarrhoea pose almost insurmountable problems and are best avoided. On one occasion I became involved in a therapeutic trial and experienced the greatest difficulty in determining the end point of diarrhoea in any given child. On many occasions a mother would claim that the diarrhoea was still ‘bad’ and we would ask to see a stool, only to be informed many hours later that the child had been unable to produce a specimen. Conversely, many patients, who were reported to be ‘better’, would on observation be seen still to be producing liquid stools. In such situations precise definition of what constitutes ‘diarrhoea’ is still largely lacking, and this is a big problem.

Secondly, I think we should mention three rather significant organisms that may otherwise not be discussed in this symposium. Entamoeba histolytica in childhood is becoming a major problem. In Cape Town, where I did my undergraduate training and where we hardly ever saw amoebiasis in childhood, a recent report from the Red Cross Hospital indicates that it was the commonest pathogen detected in 15 000 children with diarrhoea (Watson et al. 1970). The same is true of South and Central America, in many areas where this infection is on the increase (Duque 1969). In the UK, moniliasis in infants, whether antibiotic-related or otherwise, is now a problem. Thirdly, Giardia lamblia keeps cropping up in odd places in acute or chronic forms.

Children presenting with diarrhoea may be found to have more than one pathogen or potential pathogen in their stools. In many countries abroad this tends to be the rule rather than the exception. Thus, you may have a child with diarrhoea who is found to have a pathogenic E. coli or shigella infection, but has parasites like giardia in his stools and concurrent moniliasis, and one has to ask: ‘what is causing what?’ This is a problem which faces paediatricians the world over. What do you blame for the symptoms, and which do you treat?

As far as the pattern of electrolyte disturbance goes, hypernatraemia is a major problem in Europe but 90–95% of children presenting with dehydration
in the Third World do so with a hyponatraemic or normonatraemic picture, and the approach to therapy is quite different. So, when considering management we should differentiate between the technologically advanced countries and their urban satellites in developing countries, and the rest, who constitute the much larger problem.

**Edsall:** On the question of defining diarrhoea, Dr K. W. Newell 10 years ago began a monumental study in Cali, Colombia, attempting to determine what was and what wasn't 'diarrhoea'. A report has now appeared (Mansourian et al. 1975). The point made was that, as you say, one child's diarrhoea is another child's normal, and if we want to draw a borderline it isn't going to be a sharp one. It will be very broad and hazy, and there is still room for definition of when one calls something diarrhoea.

**Cutting:** In any one child, the bowel pattern changes over the period of its childhood. Only the mother knows what is currently normal for her child. She alone can decide when an increase in number or change in nature of stools constitutes 'diarrhoea'. Admittedly her past experience will affect her attitude, and this naturally results in inconsistent reporting, but it is ultimately her 'diagnosis' that precedes any action of consultation or therapy.

My second comment concerns the importance of hypernatraemic dehydration in industrialized and tropical countries. When one compares the pattern of diarrhoea in more developed areas, for example in London (Tripp et al. 1975), with poorer communities like those in South India where I worked (Ahmed & Webb 1963; Kamath et al. 1969), one finds that the age distribution is very different. In the London series the majority of children were under six months of age and many were under three months. In India most cases of diarrhoea occur after six months and many in the second year of life. Hypernatraemic dehydration appears to be a feature of children in industrialized countries, and this may be because of the age difference and the relative immaturity of the kidneys in the younger children, or also related to the type of feeding they receive.

**Smith:** Dr Harries, you mentioned the use of antibiotics in treating *E. coli* diarrhoea in babies. As far as *E. coli* infections in animals are concerned, antibiotics are very effective. In pigs a sow may have, for example, a litter of ten, so you can do split-litter studies, giving antibiotics to half only. There antibiotics are effective. I wonder, when you suggested that antibiotics are useless in diarrhoea, whether the diagnosis was correct?

**Harries:** I did not say that antibiotics are useless. I said there is no good evidence that antibiotics or anticholinergic agents affect morbidity or mortality in infantile diarrhoea assumed to be of infective origin.

**Formal:** K. C. Haltalin et al. (1967) have shown that antibiotics have a