Review article**Rotavirus gastroenteritis**

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Gastroenteritis in childhood, especially in infancy, continues to be an important problem both in developed and developing communities. In fact, in these latter communities it assumes enormous importance in regard to both mortality and morbidity. It has been estimated that in 1975 approximately 500 million episodes of diarrhoea occurred in children in Asia, Africa, and Latin America, resulting in 5 to 18 million deaths in that year (Rohde and Northrup, 1976).

Despite the size and enormous importance of this problem, it is remarkable that up until the beginning of this decade known bacterial pathogens could only be identified in the stools of less than 20% of children with acute gastroenteritis in developed communities and less than 50% in most developing communities. Thus, in large part, acute gastroenteritis in infancy and childhood was a disease of unknown origin.

The children in whom stool culture failed to yield a known bacterial pathogen were often loosely spoken of as suffering from 'viral gastroenteritis', although there were few hard data published upon which to base such an assertion. There had been extensive studies in North America from the 1950s onwards searching for a viral aetiology, but although these had shown that adenoviruses and echoviruses could be cultured from the stools of infants with gastroenteritis, they could also be cultured from many healthy controls. Most workers in Britain considered that a viral aetiology for gastroenteritis was unproven.

Then in 1973 came the first real breakthrough in this field, when Bishop and her colleagues in Melbourne identified viral particles within the enterocytes of the duodenal mucosa taken by biopsy from 6 of 9 infants with acute gastroenteritis. Rapidly and independently, Flewett and colleagues in Birmingham (1973), and Bishop's group in Melbourne (Bishop *et al.*, 1974) described techniques to identify virus particles in the stools of children with acute gastroenteritis, using the electron microscope. These findings were rapidly confirmed in a number of countries, both developed and developing.

Then a 'battle' began, which is not yet completely resolved, of terminology in relation to naming the virus particle. Orbivirus, rotavirus, reovirus-like agent, human reovirus-like agent (HRVL), duovirus, and infantile gastroenteritis virus (IGV) all are names which have been used to describe the same particle. At present it seems that *rotavirus* is the most durable name.

Virus morphology

The virus particle found in the stools of children with acute gastroenteritis is morphologically identical to the virus particles found in the stools of infant calves with acute diarrhoea. The virus occurs in two forms. One is about 70 nm in diameter with a double-shelled capsid structure having a sharply defined circular outline with the appearance of a rim of a wheel, hence the Latin name, *rota*, a wheel. Then there are smaller rougher particles which appear to be viruses which have lost their outer shell and are about 60 nm in diameter. Empty shells are frequently seen. Electron microscopy may show large numbers of virus particles packed together or scattered virus particles. Concentrations of $>10^6$ particles per ml are necessary for the agent to be seen (Tan *et al.*, 1974).

Pathogenicity of rotavirus

Flewett (1976) pointed out that one can hardly hope to fulfil all Koch's postulates before accepting a virus particle found in the stool as a pathogen. He listed some of the evidence that may reasonably be expected. Some of these are fulfilled for this particle and include the following.

(1) *Particles found in material from patients with the disease but not from patients with other unrelated diseases.* This in general appears to be true so far for rotavirus.

(2) *Prevalence of a particle in the population coincides with the prevalence of the disease.* Again this appears to be true outside the neonatal period.

Davidson *et al.* (1975a) found no particles in controls. Rodriguez *et al.* (1977) found them in 8% of 76 control children.

(3) *Presence of the particle corresponds with the duration of the disease.* Studies to date in general support this.

(4) *Purified particles induce the disease in adult volunteers or experimental animals.* Infection induced in an adult volunteer has been shown by Middleton *et al.* (1974), and infection has been transmitted to an infant monkey (Lambeth and Mitchell, 1975). Rotavirus has been identified by electron microscopy in the duodenal mucosa, duodenal juice, and stools of children with acute gastroenteritis, but only occasionally in controls. Thus, at present there appears to be enough evidence to suggest that rotavirus is a significant pathogen causing gastroenteritis. This whole subject has recently been excellently reviewed by Schreiber *et al.* (1977).

Seasonal prevalence and geographical distribution

Rotavirus has been found both in sporadic cases and in epidemic outbreaks of acute gastroenteritis in childhood. Reports have come from the developed world including Australia, Europe, and North America but also from developing communities in Africa and Asia. Its worldwide distribution suggests that it is a pathogen of major importance. Characteristically this agent has been identified in the stools of children during the winter peak of gastroenteritis. A winter peak in the prevalence of nonbacterial gastroenteritis has been known for some time in developed countries both in the northern and southern hemisphere. As long ago as 1929, Zahorsky described winter vomiting disease, and more recently two

winter epidemics of nonbacterial gastroenteritis have been described in north-west London (Sinha and Tyrrell, 1973). A study of monthly admissions to a gastroenteritis unit in Sydney from 1961 to 1972 showed the sudden appearance of a winter peak in hospital admissions in 1964, which persisted in subsequent years (Walker-Smith, 1975).

An association between this winter peak and rotavirus in the stools has now been reported from Melbourne (Davidson *et al.*, 1975a), Toronto (Hamilton *et al.*, 1976), Washington (Kapikian *et al.*, 1976), Birmingham (Flewett *et al.*, 1973), and London (see Table 1), i.e. in cold and temperate climates. The peak prevalence may approach 80% among infants and young children during the winter months in North America (Kapikian *et al.*, 1976; Hamilton *et al.*, 1976). In some reports the virus is not found at all during the summer months but in others it falls to about a 20% level. Maiya *et al.* (1977) found rotavirus in 13 of 50 children in tropical southern India (26%), the virus being found only during the cooler months of the year. In a recent study in semitropical Northern Australia, A. C. Walker and W. C. Marshall (personal communication, 1977) have shown that infections occurred predominantly in the rainy season; 50% of children admitted to Darwin hospital with gastroenteritis in the 'wet' season were found to have serological evidence of rotavirus infection in contrast to only 13% of the children admitted in the 'dry' season. Thus, it is clear that seasonal variation may have a profound effect on the prevalence of this infection.

Pathology

Rotavirus particles have been identified by electron microscopy in the small intestinal mucosa of children with acute gastroenteritis by studies in Australia

Table 1 Monthly admissions to the gastroenteritis unit at Queen Elizabeth Hospital for Children

	Total GE	Sex		Ent <i>E. coli</i>	<i>Shigella</i>	<i>Salmonella</i>	Stools for EM*	Rota*	% Stools examined
		M	F						
August 1976	33	19	14	3	—	2	7	0	0
Sept	26	13	13	4	—	5	12	1	8
Oct	28	18	10	1	—	4	10	4	40
Nov	50	19	31	2	1	1	25	9	36
Dec	58	31	27	2	3	1	36	11	30
Jan 1977	67	42	25	2	2	1	36	18	50
Feb	52	25	27	2	—	1	26	13	50
Mar	56	32	24	1	0	0	21	3	14
April	44	25	19	4	1	0	10	2	20
May	40	21	19	4	1	0	8	1	12
June	50	27	23	0	0	1	24	3	12
July	40	25	15	0	3	1	12	0	0
Total	544	297	247	25	11	17	227	65	28

*Stools examined for rotavirus at London School of Hygiene and Tropical Medicine by Dr R. Bird.

GE = gastroenteritis; Ent *E. coli* = enteropathogenic *E. coli*; EM = electron microscopy.

(Bishop *et al.*, 1973; Holmes *et al.*, 1975), Canada (Middleton *et al.*, 1974), and Japan (Suzuki and Konno, 1975). They were found in the epithelium of the villus and the crypts (Hamilton *et al.*, 1976). With the exception of the Japanese report, the particles have not been found in the lamina propria. Rotavirus was found in the enterocytes of 6 from 9 children with acute gastroenteritis, biopsied by Bishop *et al.* (1973), 1 to 5 days after the onset of symptoms. All biopsies showed histological abnormality ranging from mild to severe but the intra-epithelial lymphocyte count was normal (Ferguson *et al.*, 1976).

The virus particles in the enterocytes were found in distended cisternae of the endoplasmic reticulum and in the cisternae between the inner and outer nuclear membranes. The microvilli were often irregular and distended. Abnormal infected enterocytes were found scattered among enterocytes which were morphologically normal. The histological abnormality had reverted to normal and the virus particles had disappeared in 3 children (Bishop *et al.*, 1973) studied after recovery some 4 to 8 weeks later.

The virus appears to characteristically invade the proximal small intestinal mucosa but necropsy studies have shown that the infection can spread along the entire length of the small intestine and even into the colon (Hamilton *et al.*, 1976). Barnes (1973), in a study of 21 children with nonbacterial gastroenteritis, found evidence of inflammation in some children in stomach, duodenum, and rectum, indicating that the disease may affect the whole gastrointestinal tract. In particular there was some inflammation of the stomach in 15 of 21 biopsied. Although rotavirus was not sought in these children it is likely many had rotavirus infection, so this study indicates that the term gastroenteritis should be retained, at least for the present.

Pathophysiology

Mavromichalis *et al.* (1977) found rotavirus in intestinal aspirate of 6 out of 8 children with gastroenteritis who had rotavirus in their stools. All 6 had abnormal xylose absorption whereas the 2 without rotavirus in the lumen were normal, suggesting small intestinal dysfunction related to mucosal damage, occurred when the virus was found in the lumen.

Little is yet known in man of the mechanism of diarrhoea in rotavirus gastroenteritis, but Hamilton *et al.* (1976) studied an animal model using a similar virus in piglets. This is a corona virus, known as the transmissible gastroenteritis virus (TGE). It produces massive diarrhoea with high faecal electrolytes some 16 to 40 hours after infection. At 40 hours they found decreased sodium and water flux, decreased

mucosal activities of disaccharidases and sodium, potassium-ATPase but normal adenyl cyclase activity. Unlike enterotoxigenic diarrhoeas such as cholera, under these experimental conditions sodium flux failed to respond to glucose. If a similar situation exists in rotavirus gastroenteritis in man, it is clear that the pathophysiology may be very different from that of the toxigenic bacterial diarrhoeas. Gould (1977) studied stool prostaglandin levels in 4 children with rotavirus gastroenteritis and 4 children with gastroenteritis but no rotavirus. In contrast to ulcerative colitis, where stool prostaglandin levels are raised, he found prostaglandin levels well within the control range in both groups of children.

Age range

Rotavirus has been found principally in the stools of children with gastroenteritis from the neonatal period up to 5 years of age, but most are under 2 years. Most studies have reported a peak between 6 months and a year (Kapikian *et al.*, 1976; Carr *et al.*, 1976; Rodriguez *et al.*, 1977), but Shepherd *et al.* (1975) found 43.3% of their children were under 6 months.

Although the disease is commonest in young children it may also occur in adults. Rotavirus has indeed been found in the stools of adults with acute gastroenteritis (von Bonsdorff *et al.*, 1976). It may also occur in adults who are symptom free (Tallett *et al.*, 1977).

Sex ratio

As in earlier reports of nonbacterial gastroenteritis where viral studies were not done (Gribbin *et al.*, 1975; Tripp *et al.*, 1977), most studies of rotavirus gastroenteritis report that boys are more often affected than girls (see Table 1). The reason for this male predominance is not yet clear, but it is most obvious in the younger children.

Incubation period

The incubation period appears to be about 48 to 72 hours (Shepherd *et al.*, 1975).

Clinical features

Most studies have described vomiting as the first symptom, often accompanied by diarrhoea but sometimes preceding it by several hours (Shepherd *et al.*, 1975). On occasion there may even be no diarrhoea. The diarrhoea is typically acute in onset and often watery in character with usually fewer

than 10 stools each day. Pyrexia is a common but not a constant feature in all reports. A concurrent upper respiratory tract infection has been documented in 42% in one report (Carr *et al.*, 1976) and in 29% in another (Rodriguez *et al.*, 1977). Most clinical reports of rotavirus gastroenteritis have described a relatively mild self-limiting illness with dehydration, usually less than 5%, present in about half or less of children admitted to hospital. Rodriguez *et al.* (1977) described dehydration in 83% of children with rotavirus gastroenteritis compared to 40% in children who did not have rotavirus in their stools, but dehydration was mostly mild to moderate. It has, however, become clear that rotavirus gastroenteritis may on occasion be associated with a much more severe illness, and even death has been reported from Canada (Hamilton *et al.*, 1976) and Australia (Bishop *et al.*, 1973). Fatal rotavirus gastroenteritis does not appear to have been documented yet in Britain.

An initial study of 30 children with rotavirus gastroenteritis from the Queen Elizabeth Hospital for Children, London, during the winter of 1974–1975 found a relatively mild illness (Shepherd *et al.*, 1975). But a second study of the winter of 1976–1977, analysing the features of 17 children, found a similar mild illness in 11, but in a further 6 found a more severe illness (French *et al.*, 1978). Ryder *et al.* (1976) in Bangladesh have indeed found rotavirus in the stools of 12 out of 22 children with severe dehydration due to diarrhoea, the degree of dehydration being comparable to that found in cholera in their experience. In southern India, Maiya *et al.* (1977) found no difference in the clinical presentation of children with gastroenteritis in whom rotavirus was found compared to those in whom a bacterial pathogen was identified or no agent recognised. Thus in developing communities rotavirus is associated with less characteristic clinical patterns.

So although rotavirus gastroenteritis seems most often to cause a relatively mild illness in developed communities, it may on occasion cause more severe disease and even death. However, it must be observed that all the reports to date have largely concerned inpatients and there are very few data available concerning the presumably clinically less severe and much commoner cases managed as outpatients.

Accompanying pathogens

Any account of the severity of the clinical disease must try and take note of the possible role of accompanying pathogens, bacterial or viral. Several reports have described a more serious illness when bacterial pathogens, especially enteropathogenic

E. coli, are also found in the stools at the same time (Shepherd *et al.*, 1975; Carr *et al.*, 1976). Madeley *et al.* (1977) found rotavirus and other bacterial and viral pathogens occurring in different stool samples from the same infants and found it difficult to determine whether one or all were significant pathogens.

Duration of illness

The duration of illness ranges between 5 days and 3 weeks (Shepherd *et al.*, 1975), usually lasting only 8 days (Tallett *et al.*, 1977). Most children present within 5 days of onset if they come to hospital.

Biochemistry and haematology

A raised blood urea on hospital admission has been described (Rodriguez *et al.*, 1977) and been related to the numbers of rotavirus in the stools (Carr *et al.*, 1976). Hypernatraemia may occur but is not characteristic. When dehydration occurs it is likely to be isotonic. Lymphocytosis may occur.

Stool microscopy

Characteristically, leucocytes are not present in the stools although they may be seen in some cases: 18% in one series (Rodriguez *et al.*, 1977).

Infectivity

It appears to be a highly contagious disease apparently spread by the faecal-oral route. Massive quantities of virus may be passed in the stools some 24 to 72 hours after infection. Outbreaks may occur in families and in institutions. In one study, 35% of parents of children with rotavirus gastroenteritis had serological or stool evidence of rotavirus infection (Rodriguez *et al.*, 1977). It is also clear that adult staff members may play a role in transmitting rotavirus infections in children's wards.

Rotavirus in neonates

A high incidence of rotavirus in the stools of asymptomatic neonates has been reported from Sydney (Murphy *et al.*, 1977) and from St. Thomas's Hospital, London (Chrystie *et al.*, 1975). Murphy *et al.* found no less than 50% of neonates by age 3 to 4 days excreting virus. Only 24% of these had diarrhoea. There was no seasonal variation. How the virus spreads in the neonatal nursery is not known but is probably environmental within the nursery.

Despite the finding of rotavirus in asymptomatic neonates, Murphy *et al.* found that significantly more neonates with diarrhoea excreted the virus than

in the symptom-free group. It does, in fact, seem likely that rotavirus can cause gastroenteritis in the neonate, as suggested by Bishop *et al.* (1976) and a clue as to why some with stool rotavirus do not get clinical disease is provided by Murphy *et al.*, who found that children who had in their stools viruses coated with an 'antibody like' material did not get diarrhoea. It is known from the work of Matthews *et al.* (1976) that breast milk and cows' milk contain nonantibody virus inhibitor and this may play a role too.

Diagnostic techniques

A number of techniques have been used. Electron microscopy of stools using negative staining has been used in many centres. This is a simple technique provided an electron microscope is available. Counter-immunoelectrophoresis is a technique to detect viral antigen in the stool (Spence *et al.*, 1975; Middleton *et al.*, 1976). It seems to be about as sensitive as the electron microscope. A third technique is serum serology using complement-fixation. This was developed by Kapikian *et al.* (1975). With rotavirus stool antigen they showed a rise in serum antibody titre with a complement fixation test using acute and convalescent sera. A related antigen, Nebraska calf diarrhoea virus, is more readily available. It is morphologically and antigenically identical to rotavirus. Indirect immunofluorescent antibody technique (Davidson *et al.*, 1975b) is difficult to perform but appears to be slightly more sensitive than the complement-fixation test.

Delayed recovery

In the first detailed report of clinical features of rotavirus diarrhoea, Shepherd *et al.* (1975) described temporary sugar intolerance in 2 of 30 children with rotavirus gastroenteritis. Carr *et al.* (1976) found 2 such cases who had associated enteropathogenic *E. coli*. 4 patients reported by Tallett *et al.* (1977) had recurrent diarrhoea but they only found 'problems with absorption of sugar in a small proportion'. Thus, so far only a low frequency of sugar malabsorption has been reported. Yet in one period in the winter of 1976-1977, Lucas *et al.* (1978) found an unusually high frequency of temporary monosaccharide malabsorption coinciding with the winter peak of gastroenteritis. 6 out of 9 children with temporary monosaccharide intolerance who were examined had rotavirus in their stools.

An association between sugar malabsorption and rotavirus would not be surprising in view of the damage to microvilli in infected enterocytes (Bishop *et al.*, 1973). In addition, it appears theoretically

possible that severe and extensive infection may temporarily damage a high proportion of lactase activity of the enterocytes and perhaps also cause a transient surface block to sugar absorption by temporarily damaging the brush border membrane as proposed by Walker-Smith *et al.* (1972), clinical severity depending on number of enterocytes damaged.

Finally, Holmes *et al.* (1976) suggested that lactase is the receptor and uncoating enzyme for rotavirus. This would mean that infants, with their high lactase levels, may be more vulnerable, helping to explain the young age of most affected individuals.

Management

It appears that some cases have been managed by intravenous fluids (Rodriguez *et al.*, 1977; Tallett *et al.*, 1977) and others by an oral glucose electrolyte mixture (Shepherd *et al.*, 1977; Carr *et al.*, 1977). Hamilton *et al.* (1976) think that more rapid cessation of diarrhoea may occur when intravenous fluids are used and little is given by mouth. Certainly Torres-Pinedo *et al.* (1966) have shown a sudden fall in stool electrolytes when milk is withdrawn from the diet of infants with gastroenteritis. There is a firm clinical impression that when intravenous fluids are given to these children, with none by mouth for a short period, recovery is rapid and uneventful. Nevertheless, it would not be our practice at present to use intravenous fluids unless the infant was 5% or more dehydrated.

In view of their animal work on the pathophysiology of acute gastroenteritis, Hamilton *et al.* (1976) have queried the value of a glucose-containing electrolyte solution in these children. They consider glucose may only be a source of calories and not have the specific benefit it has in toxigenic diarrhoeas. A sucrose electrolyte mixture has a lower osmolality and sucrose is cheaper and more readily available in the developing world. An outpatient study of its use in children with acute gastroenteritis found that it is at least as effective as a glucose electrolyte solution (Rahilly *et al.*, 1976). Clearly, further evaluation is necessary in rotavirus gastroenteritis.

Immunity

Little is known yet. Reinfection of patients has not yet been reported, although children with pre-existing antibody have become infected. There is indeed some evidence that there is more than one antigenic variety of rotavirus. Antibody levels tend to rise with age, reaching adult levels at 2 years (Kapikian *et al.*, 1976).

Infants aged 6 to 24 months appear to be more susceptible to infection regardless of the presence of antibody in their sera. The lower prevalence of rotavirus infection under 6 months may be attributable to immunity acquired from mother. Bortolussi *et al.* (1974) found normal amounts of IgA in intestinal secretions during acute illness and in convalescence.

Rotavirus and chronic diarrhoea

Shepherd *et al.* (1975) also described rotavirus in 2 children with chronic diarrhoea and since then a further 3 children with chronic diarrhoea and rotaviruses in their stools have been seen at the Queen Elizabeth Hospital for Children (see Table 2). There appears to be no other report of rotavirus excretion in chronic diarrhoea. Indeed rotavirus was not found in stools of children with protracted diarrhoea in the Gambia (Rowland and McCollum, 1977). Rotavirus may have some role in the pathogenesis of chronic diarrhoea but these 5 children had only single stool examinations and no serological studies, so the significance of identification of rotavirus in these children is not yet known. This is an important area for further research. It is possible rotavirus has a triggering role in the pathogenesis of the post-enteritis syndrome and also cows' milk protein intolerance (Harrison *et al.*, 1976).

Rotavirus and Crohn's disease

A virus with the physiochemical and growth characteristics, electron microscopical and antigenic properties of rotavirus has been found in some filtrates from resected intestine from adults with Crohn's disease (Whorwell *et al.*, 1977a). De Groote *et al.* (1977) have, however, been unable to show substantial differences in rotavirus antibody titre between patients with Crohn's disease, ulcerative

colitis, and controls. A study of 7 children with Crohn's disease at St. Bartholomew's Hospital found rotavirus complement-fixing antibody in only 3 (W. Marshall and J. Walker-Smith, unpublished, 1977, Table 3). Whorwell *et al.* (1977b) were unable to find the virus in stools of patients using immune electron microscopy. Thus, it is extremely unlikely that this virus has a primary aetiological role in this disorder, although it is possible that an acute attack of rotavirus gastroenteritis in a predisposed individual may play a precipitating role.

Conclusion

It is remarkable how much information is now available concerning an infectious agent which was unknown until 1973, yet it is obvious that there is a great deal of research to be done and hopefully this may lead to practical improvement in the continuing problem of diarrhoeal disease, both acute and chronic, throughout the world. Clinicians in the developed world who usually have a clinical situation where the specific effects of rotavirus can be assessed uncomplicated by a host of other pre-existing and complicating problems, as in the developing world, have an important responsibility to investigate the specific pathogenetic role of rotavirus in diarrhoea.

Table 3 Rotavirus complement-fixation antibody titres in childhood Crohn's disease

Case no.	Age (years)	Rotavirus CF antibody titre
6	14.6	<8
7	13.0	8
8	13.0	64
9	12.0	32
10	11.0	<8
11	9.0	<8
12	6.0	<8

Table 2 Rotavirus and chronic diarrhoea

Clinical diagnosis	Small intestinal histology	Sex	Age (m)	Duration of diarrhoea at time of detection of virus in stools (m)
Case 1 Postenteritis syndrome, monosaccharide intolerance, IgA deficiency	Normal	M	3	2
Case 2 Postenteritis enteropathy, monosaccharide intolerance	Severe partial villous atrophy	M	4	1
Case 3 Acute autoimmune haemolytic anaemia and protracted diarrhoea, monosaccharide intolerance, IgA deficiency	Mild partial villous atrophy	F	5½	1
Case 4 Postenteritis syndrome with monosaccharide intolerance	No biopsy	M	7	1
Case 5 Chronic diarrhoea ? irritable colon	No biopsy	M	17	6

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