

## Overview of viral gastroenteritis

A. Z. Kapikian

Epidemiology Section, Laboratory of Infectious Diseases, National Institute  
of Allergy and Infectious Diseases, National Institutes of Health,  
Bethesda, MD

**Summary.** Diarrheal illnesses in humans have been recognized since antiquity. Such illnesses continue to take a great toll of lives, with a disproportionately high mortality in infants and young children in developing countries. Bacteriologic and parasitologic advances made during the past century led to the discovery of the etiology of some of the diarrheal illnesses, but the etiology of the major portion remained unknown. It was assumed that viruses caused most of these illnesses because: (i) bacteria were recovered from only a small proportion of episodes, and (ii) bacteria-free filtrates were found to induce gastroenteritis in adult volunteer studies. However, an etiologic agent could not be recovered despite the “golden age” of virology in the 1950’s and 1960’s when tissue culture technology enabled the discovery of numerous cultivatable enteric viruses, none of which emerged as an important etiologic agent of gastroenteritis. The discoveries of the Norwalk virus in 1972, and of rotaviruses in 1973, both without the benefit of *in vitro* tissue culture systems, ushered in a new era in the study of the etiology of viral gastroenteritis. The Norwalk virus was found to be an important cause of non-bacterial epidemic gastroenteritis in adults and older children, and rotaviruses were shown to be the single most important etiologic agents of severe diarrheal illnesses of infants and young children in both developed and developing countries. With the major advances in the study of rotaviruses, there is a high degree of optimism that in the not-too-distant future, a rotavirus vaccine will be available. In addition, the recent molecular biologic advances in the study of the Norwalk and Norwalk-like viruses, now firmly established as caliciviruses, represent a major new horizon in the study of these viruses.

### Introduction

Although diarrheal diseases have been recognized since ancient times, having been recorded on papyrus in hieroglyphic form about 3300 B.C., their etiology has remained elusive for the most part until recently [30]. This brief overview will describe the importance of diarrheal diseases in general, and present some of the advances made in recognition of viruses as major etiologic agents of diarrheal

illnesses of all age groups, from a historical, epidemiological, virological, and vaccinological perspective.

Diarrheal diseases are important cause of morbidity in developed countries and a major cause of morbidity and mortality in developing countries worldwide. For example, during the Cleveland Family Study in the United States, infectious gastroenteritis (considered nonbacterial) was the second most common disease experience, accounting for 16% of ~ 25 000 illnesses over a period of about ten years [8]. This was translated into an average of 1.52 episodes of diarrhea per person per year, a figure that is remarkably consistent with that observed in two U.S. family studies 20 to 30 years later [12, 32]. However, deaths from diarrheal illnesses occur relatively infrequently in developed countries. For example, in the U.S., a review of vital statistics from 1973 to 1983 revealed that an average of 504 children one month to four years of age died annually from diarrheal illnesses [13].

In contrast, diarrheal diseases are a major cause of death among infants and young children in developing countries. Various estimates continue to stress the major impact of diarrheal diseases: (i) 15% to 34% of all deaths in certain countries are associated with diarrheal diseases, with the greatest toll in infants and young children [38]; (ii) ~ 450 million diarrheal episodes in infants and young children less than five years of age in Asia, Africa and Latin America, with a fatality rate of 1% to 4%, resulting in five to 18 million deaths annually [34]; (iii) three to five billion cases of diarrhea and five to ten million deaths from diarrhea during a one year period in these same regions, ranking diarrhea first

**During the two days of The  
World Summit for Children, this  
is what will happen.**  
**2,800 children will die from  
whooping cough.**  
**8,000 children will die from  
measles.**  
**4,300 children will die from  
tetanus.**  
**5,500 children will die from  
malaria.**  
**22,000 children will die from  
diarrhoea.**  
**12,000 children will die from  
pneumonia.**  
**Now you know why there's  
a summit.**

**Fig. 1.** Adaptation of UNICEF poster for The World Summit for Children, United Nations, New York, September 29–30, 1990

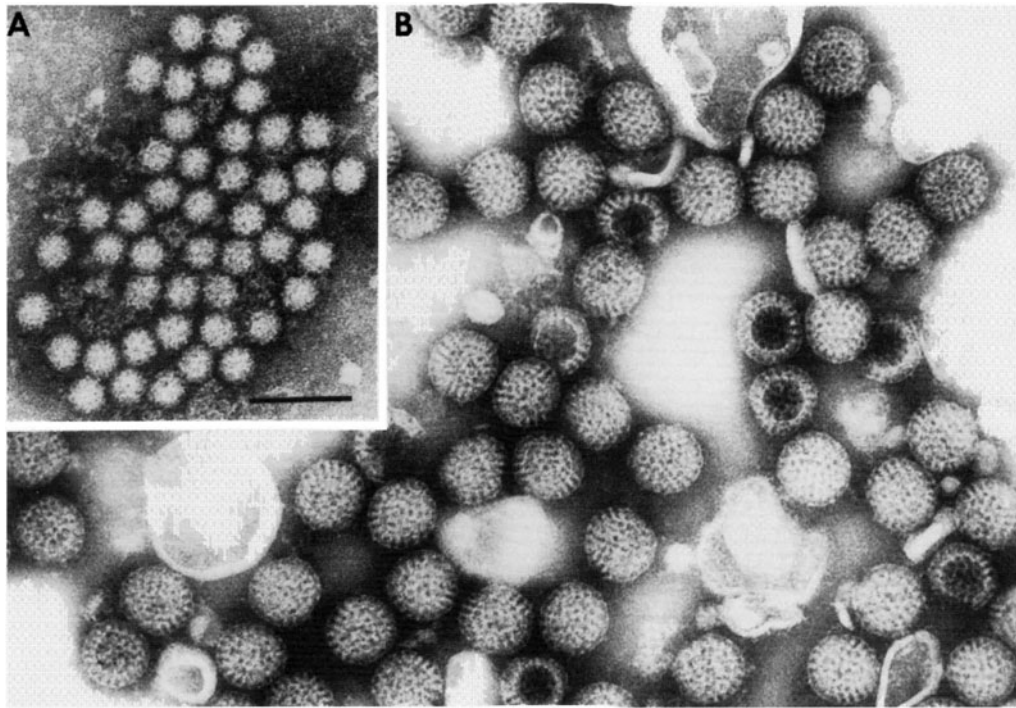
among infectious diseases with regard to frequency and mortality [37]; (iv) 744 million to 1 billion diarrheal episodes and 4.6 million deaths due to diarrhea annually in children less than five years of age in Africa, Latin America and Asia (excluding China) [35]; (v) in an update of the latter study the mortality estimates were lowered to 3.3 million deaths with a range of 1.5 to 5.1 million per year [3]; and (vi) a UNICEF poster heralding a two-day World Summit for children in 1990, at which strategies were presented to improve the health of children globally, showed in dramatic fashion the importance of diarrheal diseases, as shown in Fig. 1. Although the figures in the various estimates cited above vary widely with regard to absolute numbers, each of them lead to the same conclusion, that diarrheal diseases are a major scourge of infancy and early childhood in developing countries.

### History

Despite major bacteriologic, parasitologic, and virologic discoveries made during the past century, the etiology of most diarrheal illnesses remained unknown until the early 1970's. From the 1940's to the early 1970's, it was assumed by exclusion that viruses were the major cause because: (i) bacteria could be isolated from only a small proportion of such illnesses, and (ii) bacteria-free filtrates derived from community outbreaks of gastroenteritis induced diarrheal illness in adult volunteers in studies carried out 1945–1947 in the U.S. and Japan [21, 23]. Although bacteria-free filtrates were transmitted serially and characterized antigenically in cross-challenge studies, an etiologic agent could not be identified in any *in vitro* system. This was especially difficult to understand in the 1950's, the "golden age" of virology, when hundreds of new viruses were discovered using newly described tissue culture technology. Initially, the isolation of many distinct enteric viruses (*e.g.*, echoviruses) from infants with diarrhea was particularly encouraging, but when carefully controlled epidemiologic studies revealed that children without diarrhea shed these agents with equal frequency, their role as important etiologic agents of diarrheal illness was voided [21].

Further efforts were made in the 1960's when newer techniques such as organ culture were used successfully for the discovery of fastidious respiratory viruses, such as coronaviruses [6]. Following this lead, fecal specimens derived from outbreaks of diarrheal illness were studied in human embryonic intestinal organ culture (with the rationale that such cells were less dedifferentiated than cells passaged in tissue culture) but once again a viral agent could not be recovered [6]. It was considered that perhaps this failure was due to the absence of an infectious agent in the outbreak specimens tested. Known infectious stool filtrates from the volunteer studies of the 1940's and 1950's described above had been exhausted or were not available for study.

Therefore, adult volunteer studies were revived in the 1970's to generate known infectious stool filtrates for further study. Several gastroenteritis outbreaks were evaluated in challenge studies but one deserves special attention. A sharp outbreak of acute gastroenteritis which affected 50% of the students and



**Fig. 2.** **A** The 27-nm Norwalk virus observed by immune electron microscopy in the stool of an adult volunteer with gastroenteritis (from Kapikian *et al.* [22] [bar added]). **B** The 70-nm rotavirus observed by electron microscopy in the stool of an 11-month-old infant with gastroenteritis (from Kapikian *et al.* [23]. Bar: 100 nm (applies to A and B)

teachers in an elementary school in Norwalk, Ohio in 1968 failed to yield an etiologic agent [1]. Thus, with the aforementioned goal in mind, a bacteria-free filtrate which was prepared from a rectal swab specimen obtained from a secondary case was given orally to three adult volunteers, two of whom developed gastroenteritis one to two days after challenge (one had vomiting without diarrhea and the other had diarrhea without vomiting) [9]; serial passages in human volunteers were successful and the infectious Norwalk stool filtrate was studied for size (by filtration), acid and heat stability, and was evaluated in cross-challenge studies with other stool filtrates from other outbreaks [6, 9]. Because all efforts to propagate a viral agent *in vitro* were still unsuccessful, the indicator of infectivity remained the health-status of the volunteer following challenge. Thus, despite the more recent round of volunteer studies, the etiology of viral gastroenteritis was essentially at the same juncture as in the 1940's and 1950's.

However, in 1972, an important breakthrough was made when  $27 \times 32$  nm (shortest  $\times$  longest diameter) virus-like particles were discovered directly in an infectious stool filtrate derived from the Norwalk outbreak by the use of the

technique of immune electron microscopy (IEM) (Fig. 2A) [26]. This method permits the direct visualization of antigen-antibody interaction, thus facilitating or enabling the recognition and identification of a particle which: (i) does not have a distinctive morphologic appearance; (ii) is present in low titer, and (iii) is among the smallest known viruses [24]. This is accomplished by the reaction of a test specimen (*e.g.*, stool filtrate) which may or may not contain virus, with a putative specific antiserum. If the homotypic virus is present, it will be coated by specific antibodies and, depending on the antigen-antibody ratio, the immune complex will appear in the form of large or small viral aggregates or as individual entities so heavily coated with antibody that they fail to aggregate because of steric hindrance. The Norwalk virus was discovered after incubation of the infectious Norwalk stool filtrate (designated 8FIIa for laboratory purposes) with a volunteer's convalescent phase serum. Serologic evidence of infection with the Norwalk virus was demonstrated by IEM in paired pre- and post-challenge sera of four of the ill volunteers and in acute and convalescent phase sera from certain individuals from the original outbreak; from this and other evidence it was suggested that the 27 nm virus-like particles were the etiologic agents of the outbreak in Norwalk, Ohio [26]. The 27 nm Norwalk virus is considered to be the first virus to be identified as an important etiologic agent of viral gastroenteritis in humans. It represents the prototype strain of a group of 27 nm viruses that have still defied cultivation in any cell culture system. The technique of IEM has led to the discovery of other Norwalk-related gastroenteritis viruses such as the Montgomery County, Hawaii and Snow Mountain viruses [21, 23]. These gastroenteritis viruses are usually named after the location of the outbreak from which they were derived.

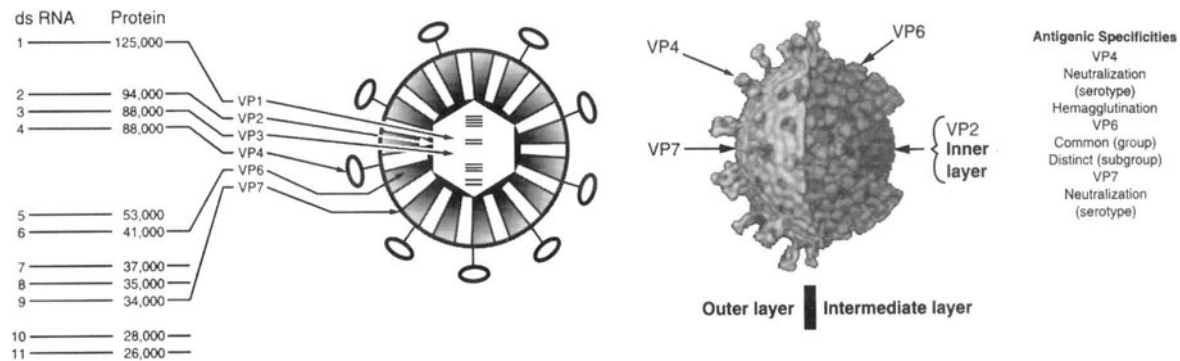
One year later, another important breakthrough occurred when the 70 nm rotaviruses were discovered by thin section electron microscopy in biopsies of duodenal mucosa in two of four children under three years of age with acute gastroenteritis [4]. It was suggested that the virus-like particles were the cause of the gastroenteritis in these two children. These EM studies were prompted by prior light microscopic investigations which had demonstrated histologic changes in duodenal mucosa of children hospitalized with acute nonbacterial gastroenteritis [2]. Shortly after the initial virus positive biopsies were reported, rotaviruses were visualized by EM in additional duodenal biopsies and soon thereafter also in feces of infants and young children hospitalized with diarrhea [5, 22]. In a relatively short time, laboratories around the world reported the presence of rotavirus particles in feces of a major segment of infants and young children with diarrheal illness and it became apparent from cross-sectional studies that rotaviruses were indeed the long sought-after major etiologic agents of severe diarrhea of this age group (Fig. 2B) [21, 23]. Thus, following a long fallow period, within a span of one year (reports in Nov., 1972 and Nov., 1973, respectively) the Norwalk virus, a major cause of epidemic gastroenteritis of adults and older children, and rotaviruses, the major cause of severe gastroenteritis of infants and young children, were discovered, paving the way for many of the studies presented in this issue.

### Norwalk and Norwalk-like viruses

The Norwalk virus is the prototype strain of a group of nonenveloped 27 nm viruses associated with epidemic gastroenteritis. These viruses: (i) have resisted all attempts to propagate them in tissue culture; (ii) are shed in feces; (iii) produce illness only in humans; (iv) infect only chimpanzees among numerous animal models studied; (v) have a positive-sense single-stranded RNA genome; and (vi) have a buoyant density of 1.33 to 1.41 g/cm<sup>3</sup> in CsCl<sub>2</sub> [23]. By EM, they display a feathery outer edge and do not have a definitive surface substructure, although in certain orientations they have suggestive surface indentations, somewhat reminiscent of caliciviruses (Fig. 2A). There are at least four distinct serotypes as demonstrated by IEM or SPIEM: these are designated Norwalk, Hawaii, Snow Mountain, and Taunton viruses according to the location from which each is derived [23]. Related “27 nm” viruses include the Montgomery County, Southampton, Desert Storm, Toronto, and Otofuke viruses [23].

Another major advance was achieved in 1990 when the Norwalk virus genome was cloned and the capsid protein expressed in a baculovirus system, forming virus-like particles [17]. Subsequently, as expression of other members of this group, followed by sequencing studies gained momentum, knowledge regarding the genetic relatedness of these viruses became available [23]. Although the Norwalk group does not display the distinctive cup-like surface indentations of the classical caliciviruses (calix = cup in Latin), on the basis of their genome organization, the Norwalk and related viruses are classified in the genus *Calicivirus* in the family *Caliciviridae*. It should be noted that other noncultivable small round structured viruses (SRSVs) have been visualized in stools of pediatric or elderly patients with gastroenteritis, some of which have the “classical” calicivirus morphologic appearance by EM; their role as important etiologic agents of epidemic or sporadic gastroenteritis has not been established [23].

The Norwalk and related viruses are transmitted by the fecal-oral route; it is possible that airborne transmission occurs under special circumstances [21, 23]. The virus has also been visualized in vomitus [10]. The Norwalk and related viruses are major etiologic agents of acute epidemic nonbacterial gastroenteritis that affects adults, school-aged children and family contacts but they do not have an important role in the etiology of diarrhea of infants and young children [21, 23]. These outbreaks occur in all seasons of the year in various settings such as cruise ships, camps, schools, institutions, and families. Foods such as raw oysters, cake frosting, salads (as well as water and commercial ice) have been incriminated as the vehicle of transmission. In systematic studies of outbreaks, most of which were selected because they were non-bacterial, the Norwalk virus was associated with 42% of 74 that occurred from 1976 to 1980 [18]. In addition, it was estimated that almost 10% of 558 unselected outbreaks of gastroenteritis (occurring from 1975–1981) were likely caused by the Norwalk virus [27]. The prevalence of serum antibody to Norwalk virus is quite different in developed and developing countries: antibody acquisition proceeds more



**Fig. 3.** Left: Schematic representation of the rotavirus particle. Right: Surface representations of the three-dimensional structures of the outer layer of the complete particle (left) and a particle (right) in which the outer layer and a small triangular portion of the intermediate layer have been removed exposing the inner layer. Modified from Kapikian and Chanock, [20]. The three-dimensional figure on the right is from courtesy of B.V.V. Prasad

slowly in former than in the latter countries, probably reflecting differences in sanitary conditions [21, 23]. Immunity to Norwalk virus remains a perplexing issue because susceptibility correlates inversely with serum or local jejunal antibodies [21, 23].

The Norwalk and related viruses do not play an important role in severe infantile diarrhea. They may be associated with mild gastroenteritis in infants and young children in certain settings [21, 23]. Unexplained at this time is the surprisingly high rate of Norwalk virus infection observed in infants and young children (49% of 154) in Finland over a period of almost two years, when sequential sera were studied by an enzyme immunoassay using the Norwalk virus outer capsid virus-like particle as antigen. However, these infections could not be associated retrospectively with illness [31].

### Rotaviruses

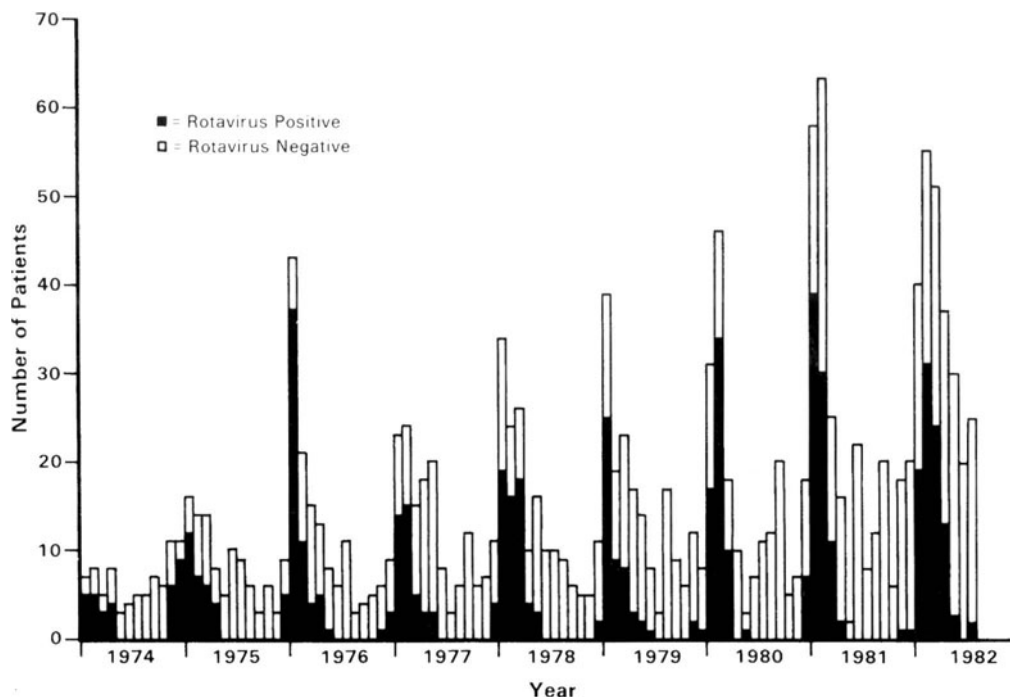
Rotaviruses are classified as genus *Rotavirus* in the family *Reoviridae*. They are 70 nm in diameter, non-enveloped, and possess a distinctive double-shelled icosahedral outer shell (Fig. 2B). Within the inner shell is a third layer, the core, which encloses the virus genome, comprised of eleven segments of double-stranded RNA (Fig. 3) [22]. Rotaviruses possess three important antigenic specificities: group, subgroup and serotype. Group specificity is mediated predominantly by VP6 (encoded by gene 6); seven groups (A–G) are recognized with groups A, B and C found in humans and all seven groups in animals [14, 22]. Subgroup specificity is also determined by VP6 (encoded by gene 6); most human rotaviruses belong to subgroup I or II. Serotype specificity has been defined until recently exclusively by VP7 (encoded by gene 7, 8 or 9 depending on the strain) [14]. VP7, a glycoprotein, is one of two major neutralization antigens located on

the outer shell. The other outer shell protein VP4 (encoded by gene 4) protrudes from the outer surface in the form of 60 spikes each 10–12 nm in length [33]. Antibodies to VP7 or VP4 are independently associated with protection against rotavirus illness [14]. The human group A rotaviruses, which are the most widely distributed rotaviruses, are further subdivided into ten human serotypes according to VP7 (or “G” [for glycoprotein]) specificity [14]. G serotypes 1, 2, 3, and 4 have consistently been shown to be the only strains of epidemiologic importance and for this reason vaccines are aimed at preventing severe diarrhea caused by these four serotypes. A serotyping system which also recognizes VP4 (or “P” [for protease sensitivity]) has been described recently and different numbers have been assigned according to neutralization specificity or genotype, giving rise to considerable confusion. A unified numbering system is under development but serotype numbers according to neutralization should have precedence to conform to standards established for other viruses [14].

Rotaviruses are the single most important etiologic agents of severe diarrhea of infants and young children world-wide [21, 22]. Infections with these agents are widespread in both developed and developing countries as evidenced by the prevalence of serum antibodies in ~90% of infants and young children by three years of age. Although rotavirus infections are known to be transmitted by the fecal-oral route, the extremely high rate of infection in both developed and developing countries, regardless of sanitary conditions, has led to speculation that respiratory transmission might also occur [21, 22]. The consequences of rotavirus infections are dramatically different in these different settings. For example, it is estimated that: (i) three million infants and young children develop rotavirus diarrhea yearly in the U.S.; (ii) 82 000 are admitted to the hospital with rotavirus diarrhea; and (iii) rotavirus diarrhea causes about 150 deaths [15]. In contrast, in developing countries, the toll is staggering. Estimates indicate that each year 18 million cases of moderately severe or severe rotavirus diarrhea occur in children under five years of age and that more than 870 000 children in this age group die because of rotavirus diarrhea [16].

In cross sectional studies in developed countries, rotaviruses are responsible for ~35 to 52% of acute diarrheal illnesses that require hospital admission of infants and young children. For example, at the Children’s Hospital National Medical Center in Washington, DC, in a period of > 8 years, 34.5% of 1537 infants and young children hospitalized with diarrhea shed rotavirus in stool specimens (Fig. 4) [7]. In a similar study in Japan, 45% of 1910 infants and young children admitted with diarrhea shed rotavirus in a period > 6 years [29]. Rotavirus illnesses occur almost exclusively during the cooler seasons of the year in temperate climates. In the tropics, rotavirus diarrhea occurs throughout the year with less pronounced peaks. Rotavirus diarrhea occurs most frequently in children between six and 24 months of age, with the next highest frequency being in the < 6 month age group [21, 22]. Neonates experience a low rate of rotavirus diarrhea, even though in certain nurseries infections may occur frequently. Adults develop subclinical infections frequently, usually without clinical manifestations [22]. Rotavirus gastroenteritis has been observed in elderly residents

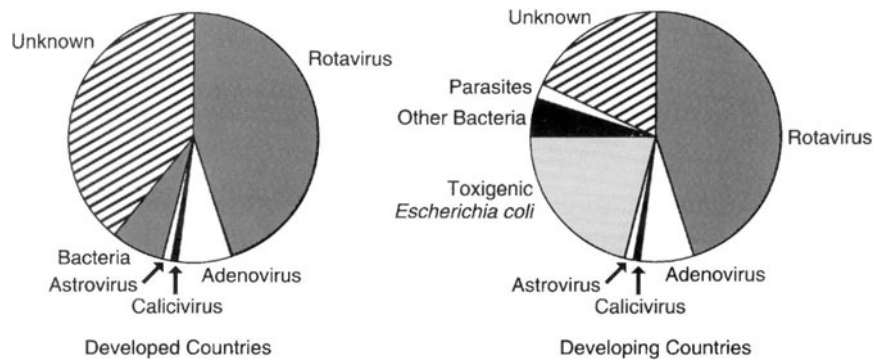




**Fig. 4.** Rotavirus infections in patients with gastroenteritis January 1974–July 1982 (as demonstrated by EM, IEM and rotavirus confirmatory ELISA) (from Brand et al. [7])

of nursing homes with several fatalities reported, but these viruses do not appear to be a major cause of morbidity in such settings [22]. The mechanism of immunity to human rotaviruses remains controversial, although in certain studies serum antibodies correlate with protection [21, 22].

Because rotaviruses are an important cause of severe illness and hospitalization in infants and young children in developed countries and a major cause of mortality in this same group in developing countries, the development of a rotavirus vaccine has received high priority from the international community [14, 21, 22]. Major efforts are aimed at developing a live, attenuated oral vaccine for administration during early infancy when the clinical manifestations of rotavirus illness are most severe. The most widely studied approach has been the “Jennerian” and “modified Jennerian” strategy in which an animal rotavirus that is antigenically related to group A rotaviruses, and human rotavirus-animal rotavirus reassortants are combined to form a four component vaccine that has VP7 antigenic specificity for each of the four epidemiologically important serotypes [19]. This quadrivalent vaccine is comprised of a rhesus rotavirus representing VP7 serotype 3, and three reassortant rotaviruses each containing ten rhesus rotavirus genes and a single human rotavirus gene that codes for VP7 serotype 1, 2, or 4 specificity [14, 20, 22]. Another vaccine, which is bovine rotavirus-based, is also under evaluation [36]. These vaccines are described later in this issue.



**Fig. 5.** An estimate of the role of etiological agents in severe diarrheal illnesses requiring hospitalization of infants and young children in developed and developing countries (from Kapikian [18])

**Table 1.** Viruses associated with acute gastroenteritis in humans<sup>a</sup>

Virus	Size, nm	Epidemiology	Important as a cause of hospitalization
Rotavirus Group A	70	Single most important cause (viral or bacterial) of endemic severe diarrheal illness in infants and young children worldwide (in cooler months in temperate climates)	Yes
Group B	70	Outbreaks of diarrheal illness in adults and children in China	No
Group C	70	Sporadic cases and occasional outbreaks of diarrheal illness in children	No
Enteric adenovirus	70–80	Second most important viral agent of endemic diarrheal illness of infants and young children worldwide	Yes
Norwalk virus and Norwalk-like viruses	27–32	Important cause of outbreaks of vomiting and diarrheal illness in older children and adults in families, communities, and institutions, frequently associated with ingestion of food	No
Caliciviruses	28–40	Sporadic cases and occasional outbreaks of diarrheal illness in infants, young children, and the elderly	No
Astroviruses	28	Sporadic cases and occasional outbreaks of diarrheal illness in infants, young children, and the elderly	No

<sup>a</sup> From Kapikian, Ref. 18

### Other agents

Various other viruses, such as adenoviruses, astroviruses, and classical caliciviruses, have been described as etiologic agents of diarrhea of infants and young children [21, 23]. Enteric adenoviruses are considered to be the second most important group of viruses associated with severe diarrheal illness of infants and young children requiring hospitalization, with estimates ranging from 3–10% [11]. The morphologically classical caliciviruses, and the astroviruses have not been shown to be important causes of severe gastroenteritis of infants and young children [21]. Toxigenic *E. coli* are an important cause of diarrhea of infants and young children in developing countries [18]. As determined from published data, an estimate of the role of various microbial agents in severe diarrhea in developed and developing countries is shown in Fig. 5 [18]. In addition, Table 1 summarizes various salient points described in this brief review of etiologic agents of viral gastroenteritis. Other viral agents, such as the toroviruses and coronavirus-like objects observed by EM in stools, await further study before they can be evaluated as etiologic agents of diarrhea in humans [21].

### Conclusion

Major advances have been made over the past two decades in elucidating the etiologic agents of viral gastroenteritis. For one of these, the rotaviruses, an effective vaccine may be available soon. However, as seen in Fig. 5, there is still a fairly substantial void in our knowledge regarding the etiology of severe diarrhea of infants and young children. Perhaps, by the time of the next international symposium on viral gastroenteritis, the etiologic “pie” will have neared completion.

### References

1. Adler I, Zickl R (1969) Winter vomiting disease. *J Infect Dis* 119: 668–673
2. Barnes GL, Townley RRW (1973) Duodenal mucosal damage in 31 infants with gastroenteritis. *Arch Dis Child* 48: 343–349
3. Bern C, Martines J, De Zoysa I, Glass RI (1992) The magnitude of the problem of diarrhoeal disease: A ten-year update. *Bull WHO* 70: 705–714
4. Bishop RF, Davidson GP, Holmes IH, Ruck BJ (1973) Evidence for viral gastroenteritis. *N Engl J Med* 289: 1096–1097
5. Bishop RF, Davidson GP, Holmes IH, Ruck BJ (1973) Virus particles in epithelial cells of duodenal mucosa from children with viral gastroenteritis. *Lancet* 2: 1281–1283
6. Blacklow NR, Dolin R, Fedson DL, Dupont H, Northrup RS, Hornick RB, Chanock RM (1972) Acute infectious nonbacterial gastroenteritis: etiology and pathogenesis. *Ann Intern Med* 76: 993–1008
7. Brandt CD, Kin HW, Rodriguez WJ, Arrobio JO, Jeffries BC, Stallings EP, Lewis C, Miles AJ, Chanock RM, Kapikian AZ, Parrott RH (1983) Pediatric viral gastroenteritis during eight years of study. *J Clin Microbiol* 18: 71–78
8. Dingle JH, Badger GF, Jordan WS (1964) Illness in the home: a study of 25 000 illnesses in a group of Cleveland Families. Western Reserve University Press (1964), Cleveland, Ohio, pp 19–32

9. Dolin R, Blacklow NR, DuPont H, Formal S, Buscho RF, Kasel JA, Chames RP, Hornick R, Chanock RM (1971) Transmission of acute infectious nonbacterial gastroenteritis to volunteers by oral administration of stool filtrates. *J Infect Dis* 123: 307–312
10. Greenberg HB, Wyatt RG, Kapikian AZ (1979) Norwalk virus in vomitus. *Lancet* 2: 55
11. Grimwood K, Carzino R, Barnes GL, Bishop RF (1995) Patients with enteric adenovirus gastroenteritis admitted to an Australian pediatric teaching hospital from 1981 to 1992. *J Clin Microbiol* 33: 131–136
12. Guerrant RL, Hughes JM, Lima NL, Crane J (1990) Diarrhea in developed and developing countries: magnitude, special settings, and etiologies. *Rev Inf Dis* 12: S41–S50
13. Ho M-S, Glass RI, Pinsky PF, Young-Okoh N, Sappenfield WM, Buehler JW, Gunter N, Anderson LJ (1988) Diarrheal deaths in American children – are they preventable? *JAMA* 260: 3281–3285
14. Hoshino Y, Kapikian AZ (1994) Rotavirus vaccine development for the prevention of severe diarrhea in infants and young children. *Trends in Virology* 2: 242–249
15. Institute of Medicine. Prospects for immunizing against rotavirus. In: *New Vaccine Development. Establishing Priorities. Diseases of Importance in the United States*, vol 1. National Academy Press, Washington, DC, pp 410–423, 1985
16. Institute of Medicine. The prospects for immunizing against rotavirus. *Establishing Priorities. Diseases of Importance in Developing Countries*, vol 2. National Academy Press, Washington, DC, pp 308–316, 1985
17. Jiang X, Graham DY, Wang K, Estes MK (1990) Norwalk virus genome cloning and characterization. *Science* 250: 1580–1583
18. Kapikian AZ (1993) Viral gastroenteritis. *JAMA* 269: 627–630
19. Kapikian AZ (1994) Jennerian and modified Jennerian approach to vaccination against rotavirus diarrhea in infants and young children: an introduction. In: Kapikian AZ (ed) *Viral Infections of the Gastrointestinal Tract*. Marcel Dekker, NY, pp 409–417
20. Kapikian AZ (1994) Rhesus rotavirus-based human rotavirus vaccines and observations on selected non-Jennerian approaches to rotavirus vaccination. In: Kapikian AZ (ed) *Viral Infections of the Gastrointestinal Tract*. Marcel Dekker, NY, pp 443–470
21. Kapikian AZ, Viral gastroenteritis. In: Evans AS, Kaslow R (eds) *Viral infections of Humans*, 4th edn (in press)
22. Kapikian AZ, Chanock RM (1996) Rotaviruses. In: Fields BN, Knipe DM, Howley PM, Chanock RM, Melnick JL, Monath TP, Roizman B, Straus SE (eds) *Virology*, vol 2. Lippincott-Raven Publishers, Philadelphia, pp 1657–1708
23. Kapikian AZ, Estes MK, Chanock RM (1996) Norwalk group of viruses. In: Fields BN, Knipe DM, Howley PM, Chanock RM, Melnick JL, Monath TP, Roizman B, Straus SE (eds) *Virology* pp 783–810
24. Kapikian AZ, Feinstone SM, Purcell RH, Wyatt RG, Thornhill TS, Kalica AR, Chanock RM (1975) Detection and identification by immune electron microscopy of fastidious agents associated with respiratory illness, acute nonbacterial gastroenteritis, and hepatitis A. *Perspect Viral* 9: 9–47
25. Kapikian AZ, Kim HW, Wyatt RG, Rodriguez WJ, Ross S, Cline WL, Parrott RH, Chanock RM (1974) Reovirus-like agent in stools: association with infantile diarrhea and development of serologic tests. *Science* 185: 1049–1053
26. Kapikian AZ, Wyatt RG, Dolin R, Thornhill TS, Kalica AR, Chanock RM (1972) Visualization by immune electron microscopy of a 27 nm particle associated with acute infectious non-bacterial gastroenteritis. *J Virol* 10: 1075–1081
27. Kaplan JE, Feldman R, Campbell DS, Lookabaugh C, Gary GW (1982) The frequency of a Norwalk-like pattern of illness in outbreaks of gastroenteritis. *Am J Public Health* 72: 1329–1332

28. Kaplan JE, Gary GW, Baron RC, Singh N, Schonberger LB, Feldman R, Greenberg HB (1982) Epidemiology of Norwalk gastroenteritis and the role of Norwalk virus in outbreaks of acute nonbacterial gastroenteritis. *Ann Intern Med* 96: 756–761
29. Konno T, Suzuki H, Katsushima N, Imai A, Tazawa F, Kutzuzawa T, Kitaoka S, Sakamoto M, Yazaki N, Ishida N (1983) Influence of temperature and relative humidity on human rotavirus infection in Japan. *J Infect Dis* 147: 125–128
30. Kumate J, Isibasi A (1986) Pediatric diarrheal diseases: a global perspective. *Pediatr Infect Dis* 5: 521–528
31. Lew JF, Valdesuso J, Vesikari T, Kapikian AZ, Jiang X, Estes MK, Green KY (1994) Detection of Norwalk virus or Norwalk-like virus infections in Finnish infants and young children. *J Infect Dis* 169: 1364–1367
32. Monto AS, Koopman JS (1980) The Tecumseh study. XI. Occurrence of acute enteric illness in the community. *Am J Epidemiol* 112: 323–333
33. Prasad BV, Burns JW, Marietta E, Estes MK, Chiu W (1990) Localization of VP4 neutralization sites in rotavirus by three-dimensional cryo-electron microscopy. *Nature* 343: 476–479
34. Rohde JE, Northrop RS (1976) Taking science where the diarrhea is. In: *Acute diarrhoea in childhood*. Ciba Foundation Symposium 42 (new series). Amsterdam, Excerpta Medica 339–366
35. Snyder JD, Merson MH (1982) The magnitude of the global problem of acute diarrhoeal disease: a review of active surveillance data. *Bull WHO* 60: 605–613
36. Vesikari T (1994) Bovine rotavirus-based rotavirus vaccines in humans. In: Kapikian AZ (ed) *Viral Infections of the Gastrointestinal Tract*. Marcel Dekker, New York, pp 419–442
37. Walsh JA, Warren KS (1979) Selective primary health care. An interim strategy for disease control in developing countries. *N Engl J Med* 301: 967–974
38. World Health Organization (1973) Mortality due to diarrheal diseases in the world. *WHO Weekly Epidemiol Rev* 48: 409–416

Author's address: A. Z. Kapikian, M. D., Epidemiology Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, U.S.A.