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Viral Gastroenteritis

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Acute gastroenteritis is a problem encountered daily by physicians. Gastroenteritis is frequently termed viral gastroenteritis if no bacterial or protozoan pathogens can be demonstrated or if bacteria-free filtrates of diarrheal stools induce the disease. The more direct diagnostic procedures currently available indicate that the majority of acute diarrheal episodes in infants and young children are of a viral origin.[112] In the developed countries acute gastroenteritis is second only to the common cold in frequency of occurrence, accounting for significant misery and expense.[20] The illness can be serious and even life-threatening in the debilitated, the elderly, and the young patient. The two most frequently implicated viruses are rotavirus and the Norwalk-like viruses. Rotavirus has consistently been associated with 50 to 70 per cent of the winter-associated gastroenteritis in children, and the Norwalk-like viruses have been implicated in large outbreaks of gastroenteritis in children and adults. The World Health Organization recently compiled the data from 24 longitudinal, prospective, community-based studies to assess the magnitude of the global problem of acute diarrheal disease.[190] In 1980 in Africa, Asia (excluding China), and Latin America there were 4.6 million gastroenteritis-related deaths in children under five years of age (Table 1).

Several enteric viruses have transiently been proposed as candidate gastroenteritis viruses. Yet these viruses, although readily isolated through cell culture techniques, have not proven to be major etiologic agents for gastroenteritis. However, since their discovery in 1972, the Norwalk-like viruses and the rotaviruses have been established as major viral gastroenteritis agents. These viruses are very fastidious with respect to in vitro cultivation and thus had not been detected through standard viral isolation procedures. Both were originally detected by electron microscopy, a technique that continues to prove very useful for establishing the etiology of gastroenteritis. In addition to the Norwalk-like viruses and the rotaviruses, there are several other viruses that now appear to be etiologic

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Table 1. *Diarrheal Morbidity and Mortality in 1980 for Children under Five-Years of Age in Africa, Asia (Excluding China), and Latin America**

Population under five years of age (in millions)	338
Annual diarrheal morbidity rate (episodes/child)	2.2
Diarrheal illnesses/year (in millions)	744
Diarrheal mortality rate (deaths/1000 children)	13.6
Diarrheal deaths/year (in millions)	4.6
Case-fatality ratio (deaths/100 episodes)	0.6

*Adapted from Snyder, J. D., and Merson, M. H.: The magnitude of the global problem of acute diarrheal disease: A review of active surveillance data. Bull. WHO, 60:605, 1982.

agents of gastroenteritis. These viruses include adenoviruses, astroviruses, caliciviruses, coronaviruses, and a group of poorly defined agents referred to as the small, round viruses. However, at this time the Norwalk-like viruses and rotaviruses appear to be the major viral agents associated with gastroenteritis.

The subject of viral gastroenteritis has been frequently reviewed.[20, 23, 83, 159, 181, 211] Other review articles deal specifically with the Norwalk-like viruses[21] and the rotaviruses.[72, 112, 193]

ROTAVIRUSES

In 1969 Mebus et al. reported that a reovirus-like agent was associated with severe diarrhea in newborn calves.[150] Numerous viral particles, 65 nm in diameter, were present in the feces; these viruses differed morphologically both from the reoviruses and orbiviruses. Procedures based on immunofluorescence were developed for diagnosis, and the virus was adapted to cell culture,[149] which later led to an oral, live-type bovine vaccine.[152] These reports received little attention outside of veterinary medicine until 1973, when a morphologically identical and serologically related virus was found in the epithelial cells of duodenal biopsy specimens from Australian children with acute nonbacterial gastroenteritis.[15] Almost simultaneously, similar reports appeared in England and Canada.[67, 153] Similar viruses have also been found to be associated with gastroenteritis in a wide range of animal species.[72] The early literature describing this group of viruses is somewhat confusing as a result of the many names used to describe them, such as reovirus-like,[71, 106, 110] orbivirus,[15, 95, 153] duovirus,[53] infantile gastroenteritis virus,[90, 141, 166] and infantile enteritis virus.[96, 178] The International Committee on Taxonomy of Viruses has placed this group of viruses in a new genus called rotaviruses, to be included with the reoviruses in the family Reoviridae.[144] The name reovirus is an acronym for "respiratory enteric orphan" (orphan because of no apparent association with a disease). As a result of their wheel-like appearance, the term *rotavirus* (from the Latin *rota*, a wheel) was suggested for this new genus of viruses.[68]

Properties of the Rotaviruses

Rotaviruses have a very distinctive morphology and are easily recognized in electron micrographs (Fig. 1). The intact rotavirus has a buoyant

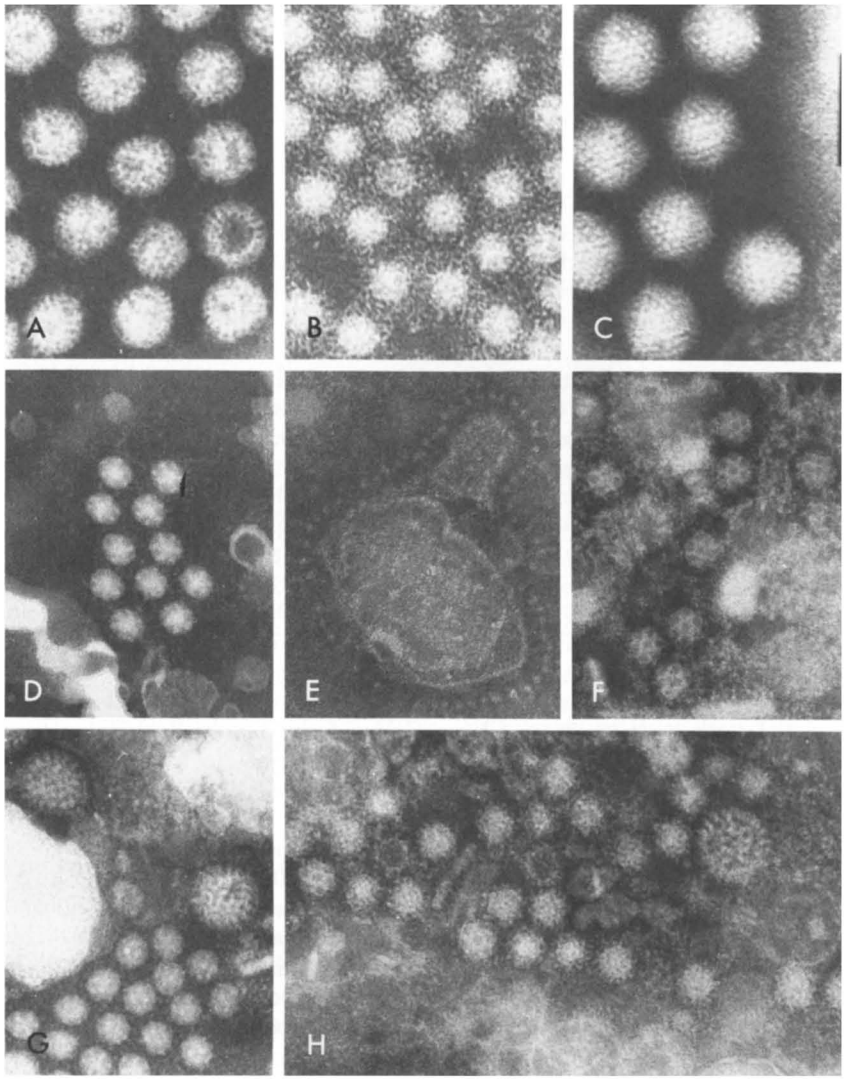

Figure 1. Viruses associated with gastroenteritis. All the electron micrographs are of viruses from diarrheic stool samples and are printed at the same magnification. *A*, Rotaviruses from an infant. *B*, Marin County Virus, a Norwalk-like virus. By immunoelectron microscopy, the fuzziness is a result of antibody coating the virus particles. *C*, Adenoviruses from an infant with gastroenteritis. The bar represents 100 nm. *D*, Astrovirus. This group of particles shows a typical star-shaped surface morphology and smooth outer edge. *E*, Coronavirus. A pleomorphic particle with pin-like surface projections around the periphery. The shafts of the "pins" are not visible, but the constant distance of the heads from the membrane confirms that they must be there. *F*, Calicivirus. The particles show cup-shaped, stain-filled hollows on the surface. *G*, Rotavirus and astrovirus. It is not uncommon to find more than one virus in a stool, and almost any combination can be found. This particular one is not uncommon, but there is no evidence to suggest that the association is anything but casual. *H*, Rotavirus, calicivirus, and small round virus. The single rotavirus and two caliciviruses are unmistakable. The reader may decide for himself whether the other particles are (a) truly virus or (b) atypical caliciviruses or a different virus altogether. (Electron micrographs A, B, and C are courtesy of Dr. L. S. Oshiro; electron micrographs D, E, F, G, and H are courtesy of Dr. C. R. Madeley.)

density in cesium chloride (CsCl) of 1.35 gm per cm^3,[61] a diameter of 68 nm,[166] and is infectious. These intact virions, sometimes called L virions,[44] consist of two layers of polypeptides surrounding a 36-nm core that contains the viral nucleic acids. When the outer polypeptide coat is absent, the resulting particle is not infectious and is referred to as the single-shelled[97] or D-particle. D-particles are frequently seen in electron micrographs of fecal specimens, having a buoyant density of 1.38 gm per cm^3 (thus the designations D for dense and L for light). Although extracellular D-particles are not infectious, the conversion of the L-particles to D-particles after entry into the host cell appears to be an obligate step in the rotaviral replicative cycle.[43]

The infectivity of rotavirus may be enhanced over 100-fold following exposure of the virus to trypsin.[11] This phenomenon of enzyme enhancement has been used to aid in the detection[32, 142, 156, 179, 186] and propagation[3, 8, 42, 78, 177, 200] of rotavirus. The mechanism of enhancement is related to the intracellular uncoating of the L-particle to the D-particle. The trypsin cleaves an 88,000 dalton structural polypeptide of the L-particle to yield a 67,000 dalton and a 21,000 dalton polypeptide, both of which remain attached to the virion. This cleavage then facilitates the intracellular conversion of the L-particle to the D-particle.[43] The trypsin-mediated enhancement of rotavirus infectivity will also occur as the ingested rotavirus passes through the digestive tract of the host.

The rotavirus genome is composed of 11 segments of linear, double-stranded RNA.[10, 104, 161, 170, 178] All members of the family Reoviridae have segmented double-stranded RNA genomes. Special electron microscopic techniques can be used to visualize the individual RNA segments being released from disrupted rotavirus particles (Fig. 2). Apparently each of these double-stranded RNA molecules is a monocistronic message specifying a viral polypeptide. One of these is a 38,000 dalton structural glycoprotein, which is the major outer capsid protein and which elicits neutralizing antibody.[63, 64, 143, 171] This polypeptide is probably coded by the eighth genome segment.[146] The eleven genome segments may be resolved by polyacrylamide gel electrophoresis and are referred to by numbers 1 to 11, in order of descending molecular weights. Virologists are particularly interested in the 38,000 dalton glycoprotein, which may hold the key to the antigenic diversity of rotaviruses and thus be of major importance in the design of a vaccine for immunoprophylaxis. In addition to this serotype-specific antigen, rotaviruses share a common group antigen demonstrable by complement fixation, immunofluorescence tests, and enzyme-linked immunosorbent assay (ELISA). This common antigen is associated with one of the inner capsid polypeptides. Recently a human rotavirus,[162] a porcine rotavirus,[26, 30] and an avian rotavirus[147] have been isolated, all lacking the common group-specific antigen. Certain strains of rotaviruses hemagglutinate human group 0 red blood cells. The gene that codes for the ability to hemagglutinate has recently been identified as the fourth genome segment,[103] which also codes for the trypsin enhancement characteristics of rotavirus and is responsible for restricting growth in cell culture. The 88,000 dalton polypeptide cleaved by trypsin[43] is probably coded by the fourth genome segment.

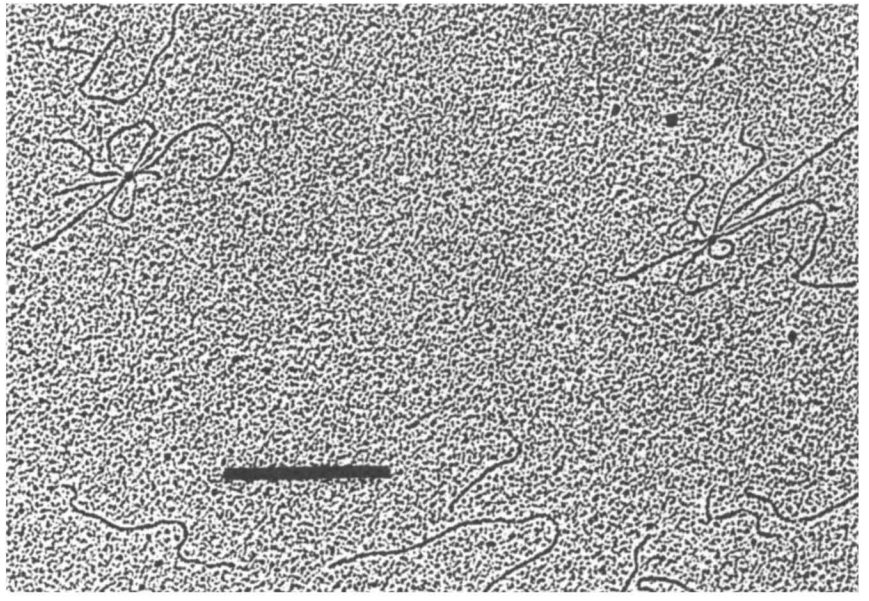

Figure 2. Electron micrograph of a rotavirus that has been exposed to 4M urea, resulting in the denaturation of the capsid proteins and the release of the double-stranded RNA genome segments. The bar represents 500 nm. (Stained with uranyl acetate and shadowed with platinum.) (*From* Barnett, B. B., Egbert, L. N., and Spendlove, R. S.: Characteristics of neonatal calf diarrhea virus ribonucleic acid. Can. J. Comp. Med., 42:46, 1978, with permission.)

Epidemiology of Rotaviral Infections

Rotaviral gastroenteritis shows both a characteristic seasonal prevalence and patient-age distribution. In temperate climates the peak period of incidence is during the winter months, with little or no rotaviral diarrhea present during the summer months.[28, 29, 94, 101, 124, 133, 155, 172] In a study based in Washington, D.C. it was reported that rotavirus was not detected at all during the summer months, yet accounted for 80 per cent or more of the gastroenteritis during December and January.[111] Brandt et al. reported that the highest prevalence of rotaviral gastroenteritis correlated with cold or dry weather as opposed to warm or wet weather.[28] They proposed that indoor crowding and low indoor relative humidity contributed to respiratory transmission of rotavirus. Konno et al. concluded that the high incidence of infection was related to cold weather but not to humidity.[126] In tropical climates the seasonal distribution may be less distinct but nevertheless apparent.[94, 139, 167, 218] In a southern Indian coastal town rotaviral diarrhea accounted for nearly 100 per cent of the November to January and 40 per cent of the April to June admissions to a pediatric diarrhea ward.[167] There was an average of 210 admissions per month, with a peak in January when 520 children were admitted.

The majority of rotaviral infections with clinical symptoms occur in children under five years of age. In a prospective study based in Winnipeg,

Canada, Gurwith et al. found that rotaviral gastroenteritis was uncommon during the first six months of life, but that 62 per cent of the infants had at least one rotaviral infection by two years of age.[88] Several hospital-based studies indicate the same general patient-age distribution of rotaviral gastroenteritis.[1, 101] An Israel-based study reported that 94 per cent of the patients with rotaviral gastroenteritis were less than 36 months of age and 35 per cent were less than six months of age.[101] In a retrospective study, Foster et al. described an epidemic of 3439 cases of rotaviral gastroenteritis in a remote Pacific island population.[74] The majority of the clinical illnesses were in the age group less than 20 years of age. The age-specific attack rates were 40 per cent in children less than one year of age, 62 per cent in the group aged one to four years, and 12 per cent in adults 20 years of age and older. Black et al. conducted a prospective study in rural Bangladesh, where the peak prevalence of rotaviral gastroenteritis was in the 6 to 11 month age group.[17] Panicker et al., from a study at a pediatric diarrhea ward in Calicut, India, reported that from 3355 cases of acute diarrhea, rotavirus accounted for 75 per cent of the cases in children 6 to 23 months of age, 65 per cent of the cases in those 24 to 60 months of age, and 35 per cent of the cases in those less than 6 months of age.

The problem of rotaviruses in neonates is somewhat cloudy. Rotavirus was found by electron microscopy in the feces of 32 per cent of the 1056 five-day-old infants in a study of newborns in English nurseries;[9, 41] however, the infection was usually asymptomatic. A similar study in New York reported no rotavirus in 925 stools from 286 neonates, even though rotavirus was present in both the hospital and the community.[194] Other reports have documented the association of rotavirus with symptomatic gastroenteritis in neonates.[33, 34]

Rotavirus is the major cause of "winter diarrhea" in infants and children; additionally there have been outbreaks of rotaviral gastroenteritis in isolated nonimmune communities involving patients from all age groups.[74, 134] Rotavirus has also caused outbreaks of gastroenteritis in school children aged 6 to 12 years.[92] Rotaviral infection in a long-stay geriatric ward affected 19 of 34 patients—6 had severe gastroenteritis and 2 died.[140] A similar rotavirus outbreak in an Oslo, Norway, nursing home for the elderly resulted in clinical symptoms in 92 of the 256 residents.[89] Again a number of the patients became severely ill and one died. A similar outbreak in a London geriatric ward has been reported.[47] In all of these instances involving geriatric patients, members of the staff also were reported ill with gastroenteritis. An outbreak in a cardiology ward also affecting the health care staff has been reported.[98] Rotavirus has also been implicated in travelers' diarrhea in adult students in Mexico[27] and in soldiers in Korea.[60] Several studies document rotaviral infection in adult contacts of pediatric patients with gastroenteritis, with the infection in adults usually mild and frequently asymptomatic.[111, 121] However, adult contacts of children infected with serotype 2 rotavirus developed clinical rotaviral illness.[174]

Clinical Manifestations of Rotaviral Infections

Shepherd et al. described a clinical study of 32 infants with rotaviral infections.[183] The incubation period was 48 to 72 hr, followed by the sud-

den onset of diarrhea and vomiting. The vomiting preceded the diarrhea by 2 to 36 hr in 47 per cent of the patients and appeared simultaneously with the diarrhea in 43 per cent. Vomiting was not a symptom in 10 per cent of the cases, although all had diarrhea. In addition to diarrhea and vomiting, fever was present in 63 per cent of the patients. Fifty-three per cent of the patients were dehydrated, usually less than 5 per cent dehydration. The recovery period was usually 5 to 7 days, the longest being 26 days. Bloody stools were not a clinical feature of the illness, and in most studies bloody stools are not observed; however, at least one report described bloody stools as a possible clinical feature of rotaviral diarrhea.[54]

The clinical features of a large epidemic of rotaviral gastroenteritis involving 3439 cases were described by Foster et al.[74] Systemic symptoms were usually absent except in young children. Symptomatic patients passed numerous (3 to 12 per day) watery brown stools (others have described offensive yellow green stools).[183] No blood or excess mucous was observed in stools. Other symptoms included fever, vomiting, and abdominal cramps. Upper respiratory symptoms (nonproductive cough) were present in 10 per cent of the patients. In younger children dehydration was common. Dehydration was a complicating factor in all seven children who died. The illness usually lasted one to four days, and all deaths occurred within the first four days of illness.

Chiba et al. described an outbreak of diarrhea in an infant home in Sapporo, Japan, wherein 42 of the 47 infants (90 per cent) were infected, and 90 per cent of those infected showed clinical symptoms.[37] Twenty-seven (64 per cent) had diarrhea, 14 per cent suffered from vomiting without diarrhea, and 12 per cent had fever ($\geq$ 38° rectal) without intestinal symptoms. The majority had diarrhea with vomiting and fever; however, in those patients under 6 months of age, vomiting was a rare symptom. The frequency of vomiting and fever increased in the older children (over 12 months of age), while diarrhea as a symptom became somewhat less common.

Black et al. noted that a greater degree of dehydration was associated with rotaviral diarrhea than with diarrhea caused by enterotoxigenic *Escherichia coli* or *Shigella*.[17] These authors speculated that because of the increased dehydration, rotavirus-associated diarrhea is more likely to result in death if rehydration treatment is not implemented. Carlson et al. described the clinical and pathologic features of 21 fatal cases of rotaviral gastroenteritis. All patients were between 4 and 30 months of age and resided in the Toronto area. Dehydration (10 to 20 per cent dehydration) and associated electrolyte imbalance were the major factors causing death; however, aspiration of vomit was believed to be the major factor in 3 of the 21 deaths. The authors' report on the autopsy and biochemical findings indicated marked dehydration as the most significant feature. Clinically, vomiting was the most characteristic symptom, occurring in all 21 patients, and was the initial symptom in 14 patients. Diarrhea was a symptom in 17 patients, while fever was noted in 10 patients. In all 21 cases, death occurred within 3 days of onset of symptoms.

A very thorough description of the clinical features of rotaviral gastroenteritis in children ill enough to require hospitalization was presented by Rodriguez et al.[172] Gurwith et al. published an equally thorough description of the clinical and epidemiologic features of rotaviral infections in

nonhospitalized children in a prospective study.[88] A summary of these two studies is presented in Table 2.

Laboratory Diagnosis of Rotaviral Infections

Rotaviral particles may be present in the feces of the infected subject at levels of 10^9 or more per gm of feces. These large numbers of viral particles allow detection by several physical or immunologic techniques. The association of rotavirus with human gastroenteritis was first demonstrated by transmission electron microscopy,[15] which remains one of the better diagnostic methods. The detection limit for rotavirus in feces is about 10^7 viral particles per ml.[123] The very distinctive morphology of rotavirus adds to the reliability of electron microscopy for this particular virus. Immune electron microscopy (IEM), similar to the conventional transmission electron microscopy except that specific antiviral serum is mixed with the sample,[2, 110] can add about 10-fold to the sensitivity of the test and greatly aids in distinguishing between artifacts and specific viral particles. Cell culture techniques in general have not proven satisfactory for detection of rotavirus. However, rotavirus may be detected by immunofluorescence if the sample is treated with trypsin and applied to the cell culture with the use of low-speed centrifugation.[12, 24, 204] Recently the combination of trypsin treatment of samples and the use of roller tube cultures of monkey kidney cells has proven satisfactory for isolating rotavirus from diarrheic fecal specimens.[177, 197, 206] ELISA is currently the method of choice for rotaviral detection in many laboratories. This procedure offers unprecedented sensitivity, specificity, and practicality for an immunodiagnostic technique.[36, 114, 191, 219, 220] ELISA is more sensitive than electron microscopy, but electron microscopy offers the advantage of detecting viruses other than rotaviruses.[182] Commercially prepared conjugates[222] and complete assay kits are available for detection of rotavirus by the ELISA procedure. A very promising development is the multiple determinant ELISA,[222] which, through the elimination of several washing and incubation steps, may be completed in 40 min as opposed to 4 hr for a conventional ELISA. The key to this assay is the use of solid phase antibody and enzyme-labeled antibody directed at different antigenic sites on the virus.

Other detection procedures for rotavirus include immunoelectroosmophoresis,[79] complement fixation,[108, 225] viral RNA electrophoresis,[7, 93] radioimmunoassay,[49, 154] and the very rapid latex agglutination technique.[176]

Immunity to Rotaviral Infection

Most individuals acquire serum antibody to rotavirus by the age of 2 years,[224] and rotaviral infections associated with illness become much less common after 5 years of age. Sequential rotaviral infections commonly occur in children under 5 years of age, but these illnesses are usually the result of infections with different serotypes of rotaviruses.[73, 111, 173, 224] Since most serologic techniques such as immunofluorescence and ELISA do not distinguish between serotypes of rotaviruses, caution must be exercised in interpreting the role of rotavirus-specific antibody in protecting against rotaviral infection. The majority of rotavirus strains from different species share common antigenic determinants (termed group antigens), which are

Table 2. *Clinical Symptoms Associated with Rotaviral Infections*

SYMPTOM	HOSPITALIZED GASTROENTERITIS PATIENTS (PER CENT HAVING SYMPTOM)*		PROSPECTIVE STUDY OF CHILDREN WITH ROTAVIRAL INFECTIONS (GENERALLY NOT HOSPITALIZED)†	
	Patients Positive for Rotaviral Infection	*Patients Negative for Rotaviral Infection*	*Symptom Present (%)*	*Symptom Occurred First (%)*
Diarrhea	100‡	100‡	65	29
Vomiting	96	58	48	34
Fever	77	61	34	13
Upper respiratory	49§	32§	52	24
Dehydration	83	40	Not reported	—

*Adapted from Rodriguez, W. J., Kim, H. W., Arrobio, J. O., et al.: Clinical features of acute gastroenteritis associated with human reovirus-like agent in infants and young children. J. Pediatr., *91*:188, 1977.

†Adapted from Gurwith, M., Wenman, W., Hinde, D., et al.: A prospective study of rotavirus infection in infants and young children. J. Infect. Dis., *144*:218, 1981.

‡Diarrhea was the parameter used for inclusion of patients in this study.

§Per cent with pharyngeal erythema.

readily detected by complement fixation, immunofluorescence, ELISA, and radioimmunoassay.[31, 49, 80, 107] Rotavirus strains from different host species have unique virus-specified surface antigens that usually are not differentiated by these procedures but that are readily distinguishable on the basis of serum neutralization assays.[14, 62, 77, 80, 207] Thus, antisera directed against rotaviruses from other species show relatively poor cross-neutralization of human rotavirus.[62, 77] There are conflicting reports on the subject of cross-protection. Wyatt et al. observed heterologous cross-protection in calves immunized in utero with bovine rotavirus and subsequently challenged as newborns with a human origin strain of rotavirus.[217] Strains of rotaviruses from humans can be divided into at least three serotypes.[84, 207, 216] The serotype specificity resides in a 38,000 dalton surface glycoprotein.[105, 146] Interestingly, this particular glycoprotein exhibits a high degree of sequence heterogeneity,[64] which may in part account for the high frequency of reinfection.

Even when the problem of multiple serotypes is taken into account, there is still a poor correlation between serum rotavirus-specific antibody levels and protection against rotaviral infection. Studies in adult volunteers have shown that rotavirus-specific, secretory IgA in the intestine is the prime correlate with resistance to rotaviral disease.[114] This protection is very serotype specific; thus, IgA antibody to serotype 1 does not protect against infection with serotype 2. Sonya and Holmes used an ELISA procedure to measure rotavirus-specific immunoglobulins of the IgA, IgG, and IgM classes in feces from patients infected with rotavirus.[191] The time course of coproantibody response to rotaviral infection was similar for all three immunoglobulin classes, appearing one to two weeks after the onset of illness, reaching peak titers two to four weeks after infection, then dropping sharply to undetectable levels after about two months. The sharp rise in coproantibody levels may play a role in the acute, self-limiting nature of most rotaviral infections, and the transient nature of this local immune response may leave the patient susceptible to a subsequent rotaviral infection.

Very little is known about the role of cell-mediated immunity in rotaviral infections. Virus-specific, cell-mediated immunity did not develop in neonatal mice infected with rotavirus.[184]

Passive Immunity

In animal studies, orally ingested antibody in colostrum, milk, or even serum has proven effective in protecting against rotaviral infection.[25, 31, 151, 188, 189, 212] These studies indicate that the antibody must be present in the gut in order to exert a protective effect. Breast feeding decreases the incidence of gastroenteritis in children and decreases the severity of the illness.[41, 51, 91, 180, 185, 203, 204] This has generally been attributed to anti-rotavirus secretory IgA, present in over 90 per cent of the colostral and milk samples tested.[223] The level of anti-rotavirus secretory IgA in colostrum is independent of antibody levels in the serum.[99] Additionally, others have reported the presence of non-immunoglobulin rotavirus inhibitory activity in milk and colostrum.[164, 165, 205] Secretory IgA antibody to rotavirus is readily detected in milk 6 months to 2 years post partum.[50, 51, 223] Although many reports indicate a protective role for breast feeding, some

studies have shown no protective effect with respect to rotaviral infections.[88]

Vaccine

Sequential rotaviral infections in the same subject are usually attributable to different serotypes of rotaviruses.[73, 173, 224] These observations are encouraging for vaccine development, since there does appear to be a naturally acquired protection against subsequent reinfection with the homologous serotype of rotavirus. Presently there is no rotavirus vaccine for human use. The prospects and problems associated with developing rotavirus vaccines have recently been reviewed.[36, 114] Much of the available evidence indicates that local immunity in the gut, such as that associated with secretory IgA, is more important than serum antibody in protecting against rotaviral disease. For this reason a high priority has been placed on the development of an oral, live-type vaccine. Attempts are underway to generate cell culture–adapted, attenuated strains of rotavirus to be tested as candidate vaccines.[114] Another approach is to isolate reassortant hybrid rotaviruses from mixed cultures of human and bovine rotaviruses. Although such hybrids have been isolated,[84] their pathogenicity and immunogenicity remain to be determined. An attenuated live-type rotavirus vaccine has been used in cattle for many years.[152] A new approach with the bovine vaccine has been to utilize maternal vaccination in order to take advantage of the subsequent transfer of passive immunity to the offspring.[187]

NORWALK-LIKE VIRUSES

There are two major epidemiologic forms of viral gastroenteritis. Rotaviruses cause sporadic, but occasionally epidemic, gastroenteritis, usually occurring during the winter months. This form primarily affects infants and young children, lasts 5 to 8 days, often leads to dehydration, and may require medical attention. The second form of gastroenteritis is more epidemic in nature, usually results in a shorter and milder illness, and occurs throughout the year in older children and adults. A group of 27-nm viruses referred to as the Norwalk-like viruses are responsible for the majority of the outbreaks of the second form. The prototype virus of this group, the Norwalk virus, was discovered in a 1968 outbreak of gastroenteritis in Norwalk, Ohio.[113] The outbreak affected 50 per cent of the students at an elementary school and 32 per cent of the family contacts. Symptoms lasted 12 to 24 hr with an apparent incubation period of 48 hr. Of the 604 subjects with symptomatic infections, 85 per cent had nausea, 85 per cent vomiting, 52 per cent abdominal cramps, 44 per cent diarrhea, and 32 per cent fever. There were no deaths, and none of the subjects were hospitalized. Other viruses morphologically similar to, but antigenically distinct from, the Norwalk virus are also etiologic agents of acute, epidemic gastroenteritis (for example, Hawaii virus,[57] Montgomery County virus,[202] Ditchling virus,[4] the W or Wollan virus,[46] the Marin County virus,[163] the Snow Mountain virus,[158] and the Parramatta virus[40]).

There are at least four antigenically distinct serotypes of Norwalk-like

viruses.[58, 159, 163, 215] A radioimmunoassay for antibody to the Norwalk virus[85] has been used to perform epidemiologic studies which indicate that the Norwalk virus causes about 42 per cent of the epidemics of acute gastroenteritis.[115] There are no comparable assays for the other three immunologically distinct serotypes; thus, their epidemiologic significance is not well understood. The high percentage of outbreaks caused by the Norwalk virus indicates that there are probably only a few serotypes responsible for acute gastroenteritis in contrast to the more than 70 serotypes of enteroviruses and the more than 100 different serotypes of rhinoviruses.[21] In studies with volunteers inoculated with the Norwalk, Hawaii, and Montgomery County (MC) viruses,[215] all of these viruses induced short-term homologous immunity, and exposure to the Norwalk virus produced partial protection against subsequent challenge with the MC virus. The Hawaii virus did not appear to be serologically related to either the Norwalk or the MC viruses. The clinical and epidemiologic features of the gastroenteritis caused by the Norwalk-like viruses are too similar to allow distinction between the viruses on these criteria. A clear picture of the epidemiologic role of each of these viruses awaits the development of suitable immunodiagnostic reagents. Between 1976 and 1980, 42 per cent of 74 outbreaks of acute nonbacterial gastroenteritis investigated by the Centers for Disease Control were caused by the Norwalk virus, and the remaining 58 per cent, based on clinical and epidemiologic data, were probably caused by antigenically distinct Norwalk-like viruses.[115]

Properties of the Norwalk-like Viruses

Because the Norwalk-like viruses are present only at low concentrations in diarrheic feces and since they have not yet been cultured in vitro, the detailed characterization of this group of viruses has not been performed. As yet we know only enough about these viruses to allow for the most tentative classification. The viral particle is round, 27-nm in diameter, and nonenveloped (see Fig. 1). The capsomeric substructure has not been clearly visualized. In most electron micrographs the virion substructure is quite hazy as a result of antibody coating the particles (a consequence of the IEM procedure). The Norwalk viruses remain infectious after exposure to pH 2.7 for 3 hr, 20 per cent ether for 24 hr, or heating at 60° C for 30 min.[56] The density of the virion in CsCl is 1.37 to 1.41 gm per ml.[109] These properties led to tentative classification as a parvovirus-like agent.[109] The paroviruses are single-stranded DNA viruses that multiply in the nucleus of the host cell. Included in the family Parvoviridae are the adeno-associated viruses, which replicate only in cells that are also infected with adenovirus, the Aleutian mink disease virus, and several parvoviruses that cause gastroenteritis in agriculturally important animals. Outbreaks of severe canine gastroenteritis associated with a parvovirus occurred suddenly in many parts of the world in 1978.[65, 145] However, it is now thought that the Norwalk viruses may not be appropriately described as parvovirus-like. When the proteins of purified Norwalk virus were analyzed by polyacrylamide gel electrophoresis, only one—a 59,000 dalton protein—was detected.[81] For the Norwalk virus to be a parvovirus, three structural proteins should have been observed. However, caliciviruses

have only one structural protein of about 65,000 daltons and share a morphologic similarity to the Norwalk virus. Caliciviruses are usually somewhat larger, 35 to 40 nm, but the fuzziness of most electron micrographs of Norwalk virus could account for a mismeasurement of their diameter. Caliciviruses are known to be associated with gastroenteritis in humans.[70, 148, 192] Caliciviruses have single-stranded RNA genomes; thus although final classification of the Norwalk viruses awaits the characterization of their nucleic acids, it is thought that they may be a type of calicivirus.

Clinical Manifestations of Norwalk-like Viral Infections

Norwalk viral gastroenteritis is usually milder than the illness caused by rotavirus. Many outbreaks of 24-hr influenza, intestinal influenza, and stomach influenza are actually Norwalk viral infections. In describing 38 Norwalk viral outbreaks, Kaplan et al. point out that only 3 persons required hospitalization.[115] However, an outbreak of Norwalk viral infection in a nursing home may have been a factor in the deaths of two patients. Norwalk viral gastroenteritis may last from 2 hr to several days, but the illness usually lasts 24 to 48 hr. The incubation period is also 24 to 48 hr. The symptoms include nausea, vomiting, abdominal cramps, diarrhea, fever, headache, and myalgias. Vomiting occurs more frequently in children, and diarrhea is more common in adults. In 6 elementary school outbreaks, 75 per cent of the ill children vomited and 46 per cent passed diarrheic stools in contrast to 4 outbreaks primarily in adults in which vomiting was a symptom in 51 per cent and diarrhea in 85 per cent.[115] In several studies adult volunteers have been challenged with Norwalk-like viruses.[20, 55, 57, 58, 196, 201] Symptoms in adult volunteers who received an oral dose of a 2 per cent stool filtrate of the original Norwalk virus closely resembled those observed in outbreaks. Thirty-three of the 55 volunteers became ill. Symptoms included anorexia in 95 per cent, headache in 84 per cent, diarrhea in 84 per cent, abdominal discomfort in 72 per cent, vomiting in 63 per cent, and fever ($\geq$ 37.4° C) in 50 per cent.[209] Bloody stools are not seen in Norwalk viral infections.

Results from small bowel biopsy specimens are consistent with the presence or absence of clinical illness. All volunteers who became ill were found to have lesions characteristic of Norwalk viral gastroenteritis, whereas no such lesions were observed in volunteers in whom clinical symptoms developed.[168] Norwalk-associated lesions include abnormal villous absorptive cells with decreased cell height and vacuolation of the cytoplasm and an increased infiltration of the lamina propria and villous epithelium with leukocytes.

Epidemiology of Norwalk-like Viral Infections

The epidemiology of Norwalk-like viral infections has been extensively studied. The explosive epidemic nature of these outbreaks tends to overshadow the relatively mild nature of the illness. Outbreaks occur year round in various settings, often associated with a vehicle such as food or water, but person-to-person transmission also plays a major role. It may be that the Norwalk-like viruses are the major cause of epidemic gastroenteritis in the developed countries. Of 74 outbreaks studied by the Centers for

Disease Control, 42 per cent were caused by Norwalk or serologically related viruses, and the remaining 58 per cent, based on clinical and epidemiologic data, probably were caused by other Norwalk-like, but antigenically distinct, viruses.[115]

Many Norwalk viral outbreaks have been associated with contaminated water supplies. There are no satisfactory procedures for detecting these viruses in water; thus coliform counts are often used as indirect evidence for possible contamination with Norwalk-like viruses. Taylor et al. described an outbreak initiated by contaminated water at an elementary school.[198] Illness developed in 72 per cent of the students and teachers. The secondary attack rate was 32 per cent in families of those who had become ill after drinking water at the school. This person-to-person secondary transmission is common for Norwalk viral infections. Several other reports of culinary water–associated outbreaks detail a similar epidemiologic picture.[116, 158, 210] Norwalk viral illness has also followed swimming exposure both in pools and lakes.[13, 118, 127] Food contaminated by Norwalk virus has also served as a vehicle; an Australia-wide outbreak of Norwalk viral gastroenteritis involving several thousand people followed the consumption of contaminated raw oysters.[160] Many other outbreaks have been associated with raw seafood and salad.[5, 86, 87] In some of these outbreaks the illness was initially referred to as food poisoning, when in fact it was the result of a Norwalk viral infection.

The efficient person-to-person transmission of Norwalk viral gastroenteritis leads one to suspect a respiratory route of transmission, but this has not been demonstrated and respiratory symptoms are usually not seen in Norwalk viral infections. However, Wilson et al. reported upper respiratory symptoms in 42 per cent of those ill in a Norwalk viral gastroenteritis outbreak at a Pennsylvania summer camp.[210]

Outbreaks in institutional settings have been reported. Kaplan et al. described an outbreak in a nursing home in which 46 per cent of the residents and staff experienced diarrhea and vomiting of acute onset. There were no serious sequelae, and none of the subjects required hospitalization. Serologic examination revealed Norwalk or Norwalk-like virus as the etiologic agent.

Norwalk virus may play a minor role in the etiology of travelers' diarrhea. A study of adult student travelers in Mexico showed that 5 to 6 per cent of them seroconverted to Norwalk virus.[120]

Diagnostic Tests for Norwalk Viral Infections

There are no satisfactory routine diagnostic tests for the Norwalk-like viruses. Conventional transmission electron microscopy has the drawbacks of insufficient sensitivity and specificity. The viruses are shed only briefly and in relatively small numbers; thus, it is very difficult to attain the required sensitivity with electron microscopy. In addition, the morphology of the Norwalk viruses is relatively nondistinct; thus, positive identification is usually not possible. Immune electron microscopy (IEM) offers a partial solution to these problems.[58, 113] IEM is more sensitive, and the use of a Norwalk-specific serum allows for positive identification of the viruses. A radioimmunoassay (RIA) for the Norwalk virus and its antibodies has been

a powerful tool for epidemiologic studies.[22, 85] Immune electron microscopy was used to detect Norwalk viruses in samples from 5 of 27 outbreaks that had been confirmed to be caused by Norwalk virus on the basis of seroconversion as determined by RIA.[115] The major problem with RIA is that only a few laboratories in the world have the required antisera and Norwalk virus antigens, which are obtained from volunteers who have been challenged with the Norwalk virus. Another problem with RIA is that it does not detect the morphologically similar, but antigenically distinct, Norwalk-like viruses.

Serology and Immunity

Norwalk viral infections occur on a worldwide basis. Greenberg et al. found that 50 to 80 per cent of adults in both developed and developing countries have serum antibody to Norwalk virus.[82] The age-related distribution of serum antibody to Norwalk virus is very distinct from that for serum antibody to rotavirus. Blacklow et al. used RIA to test sera from 308 residents of Massachusetts and found Norwalk virus antibody in 20 per cent of the infants 0 to 3 months of age (presumably of maternal origin).[22] In infants 6 months of age, Norwalk antibody was not detected, and the per cent of children with detectable anti-Norwalk virus antibody remained at 5 per cent through 8 years of age. A sharp rise in the prevalence of Norwalk virus antibody was observed in the adolescent and early adult years. Approximately 50 per cent of those over 20 years of age possessed antibody. In the developing countries antibody to the Norwalk virus is acquired much earlier in life. In a longitudinal study of young children in Bangladesh the prevalence of antibody to Norwalk virus was 7 per cent in infants younger than 6 months and increased to 80 per cent in children 2 to 5 years of age.[18]

The antigenic relationships among Snow Mountain, Hawaii, and Norwalk viruses were determined by IEM using serum antibody from previously challenged volunteers.[58] Each of the three viruses showed a strong reaction with homologous antibody, but no heterologous reactions were observed. Sera positive for antibody to the Snow Mountain virus did not react with the Marin County virus[163] in the IEM procedure.[58] Previously it had been shown that the Marin County virus does not cross-react with the Norwalk or Hawaii viruses.[163] Thus, the Norwalk, Marin County, Hawaii, and Snow Mountain viruses appear to represent four antigenically distinct serotypes of morphologically indistinguishable Norwalk-like viruses. There are several other viruses in this group that remain to be serotyped. In vivo cross-challenge studies in volunteers showed that the Norwalk virus and Montgomery County virus are serologically related, whereas there was no heterologous cross-protection between the Hawaii virus and the Norwalk virus.[215]

The subject of clinical immunity to Norwalk viral infection is very puzzling. In about 50 per cent of the volunteers inoculated with Norwalk virus, gastroenteritis and an antibody response to the infection developed.[201] However, the susceptibility does not appear to hold to the classic picture of antibody-mediated immunity. There is a short-term immunity to Norwalk infection—when previously ill volunteers were rechallenged 4

to 14 weeks after the initial illness, they remained well.[20, 23, 168] However, volunteers who previously became ill when inoculated with Norwalk virus again became ill when rechallenged after 27 months, even though they often possessed high serum- or duodenal fluid-antibody titers to Norwalk virus.[52, 168] The volunteers who did not become ill usually had no or a very low antibody titer to Norwalk virus both before and after challenge. On rechallenge 27 to 42 months later, the same volunteers who became ill the first time became ill again, and those in whom gastroenteritis did not develop on initial challenge again remained symptom-free. Factors other than antibody appear to be important in susceptibility to Norwalk viral infection. Antibody may play a role in short-term immunity, but long-term immunity appears to be independent of antibody.[168] In the case of either serum antibody or local jejunal antibody to Norwalk virus, those individuals with antibody are much more likely to be susceptible than those with little or no antibody. Susceptibility may be determined by factors such as the presence or absence of viral receptors, in which case antibody is just an indication of past infection and therefore indicates susceptibility. The paradoxical relationship of antibody to susceptibility and the lack of demonstrated long-term immunity do not forecast much hope for the development of a vaccine to prevent Norwalk viral infections.

MISCELLANEOUS VIRUSES ASSOCIATED WITH GASTROENTERITIS

Rotaviruses and Norwalk-like viruses appear to be the major etiologic agents for the two primary epidemiologic forms of acute viral gastroenteritis. However, there are several other candidate viruses.

Adenoviruses

Other than rotaviruses, adenoviruses are the most frequently observed viruses in stools from children with gastroenteritis. Many groups have observed fastidious adenoviruses on electron micrographs (see Fig. 1) in diarrheic fecal specimens.[66, 76, 100, 155, 208, 221] Unlike other adenoviruses that are easy to cultivate and type, these enteric-type (ET) adenoviruses have resisted propagation in cell culture. It was found recently that the ET adenoviruses possess a distinct set of antigenic determinants that can be detected by ELISA.[100, 221] Furthermore, these ET adenoviruses produce a characteristic cytopathic effect in a line of human embryonic kidney cells transformed by adenovirus type 5 (293 cells), but not in nontransformed human embryonic kidney cells.[195, 221] Fecal adenoviruses that are readily cultivatable by standard techniques are found with about the same frequency in subjects with or without gastroenteritis.[102, 221] However, the fastidious ET adenoviruses are highly associated with gastroenteritis in children.[138, 221] Yolken et al. examined the feces of 99 infants between the ages of 4 and 25 months while they were inpatients at a Baltimore area hospital.[221] Twenty-seven had an episode of diarrhea during the study, and ET adenovirus was identified in the stools of 52 per cent of the children with diarrhea. ET adenovirus was found in only one of 72 (1.4 per cent) children without diarrhea. The ET adenovirus–associated illnesses lasted

for a mean of 8.0 days, and the children passed a mean maximum of 8.5 stools per day. Other symptoms were upper respiratory (93 per cent), with 43 per cent having signs of pneumonia, fever (93 per cent), and vomiting (79 per cent). The epidemiology of ET adenovirus–associated gastroenteritis is not well defined. It remains to be established whether the 52 per cent association with cases of infantile gastroenteritis in the reported study is indicative of the prevalence of ET adenovirus–associated gastroenteritis.[221]

Astroviruses

Astroviruses are 28 to 30 nm in diameter with a very characteristic 5- or 6- pointed star-shaped surface structure (see Fig. 1).[39] Astroviruses have not been cultivated in vitro and their nucleic acid type is unknown; they therefore have not been classified. Several outbreaks of gastroenteritis in children, infants, and adults have been associated with astroviruses.[6, 125, 130, 136] Studies in volunteers indicate that astroviruses are transmissible but have a low pathogenicity in adults.[129] Clinical symptoms of astroviral infection in a gastroenteritis outbreak in a kindergarten in Japan (attack rate 52.3 per cent) were vomiting (64 per cent), abdominal pain (49 per cent), diarrhea (30 per cent), and fever higher than 37.5° C (30 per cent). The disease was self-limiting, the symptoms lasted an average of 12 hours, and only one of the 46 ill subjects required medical care.[125] Astroviruses are excreted in large numbers and are readily detected by electron microscopy. Identification is simplified as a result of their very characteristic morphology. IEM, using paired acute and convalescent sera and feces rich in viral particles, is useful for establishing etiology.[122, 125] However, the star-like morphology is obscured in IEM when the viruses are coated by specific antibody.[6] Astroviral antibody may be detected using indirect fluorescence and infected primary human embryo kidney cultures.[128] Most children (70 per cent) acquire astroviral antibody by 5 years of age.[128]

Enteroviruses

Enteroviruses do not appear to play a major epidemiologic role in gastroenteritis, but enteroviral disease is frequently severe in infants.[39, 131, 157] Meningitis, polio-like paralytic disease, and severe systemic disease are associated with enteroviral infections.[39, 119, 131, 157] These infections are more prevalent in the summer months. The incidence is 10 or more times greater in infants than it is in school-aged children, and nearly 100 times greater than in adults.[157]

Coronaviruses

Coronaviruses have been detected in the feces of persons with gastroenteritis.[45] The very distinctive morphology of coronaviruses makes them easy to identify. They are enveloped, about 100 nm in diameter, and possess characteristic club-shaped projections surrounding the virus like a halo or crown, hence the name (see Fig. 1). Coronaviruses are found frequently in feces from asymptomatic adults; thus, their relation to gastroenteritis is uncertain.[45] These RNA-containing viruses are associated with 5 to 10 per cent of the upper and lower respiratory tract infections in man.

Caliciviruses

Caliciviruses are recognizable by the characteristic cup-like depressions on their surface that give the impression of a 6- or 10-pointed star[135] and because of their size (31 nm to 40 nm in diameter) (see Fig. 1). Caliciviruses have been associated with several well-defined outbreaks of gastroenteritis primarily in infants and children.[38, 48, 69, 137, 148, 192] The symptoms associated with the reported outbreaks were nausea, vomiting, and diarrhea. Rising antibody titers were measured by IEM.[148] Caliciviruses spread readily, and nosocomial outbreaks have been reported.[192]

Other Viral Agents

The roles of several other ill-defined fastidious viral agents such as the minirotavirus,[192] minireoviruses,[155] and the Otofuke agent[196] remain speculative.

TREATMENT OF VIRAL GASTROENTERITIS

Most cases of viral gastroenteritis are self-limiting and only rarely require medical attention. However, in severe cases, especially in the very young or the debilitated, prompt therapy is necessary.

In an analysis of 21 fatal cases of rotaviral gastroenteritis, the primary characteristic was profound dehydration. These children were 10 to 20 per cent dehydrated at the time of death.[35] Some of these children were examined for signs of dehydration in the morning, but rapidly dehydrated through the day and succumbed by evening. Thus, the primary therapy is to maintain the proper state of hydration. Acute diarrhea may be caused by any of several bacterial, protozoan, or viral agents, yet the physiologic effects are quite similar. These include (1) dehydration, electrolyte deficiency, and acidosis; and (2) anorexia and possibly vomiting, which reduces nutrient intake.[175] Acute viral diarrhea is self-limiting and can be effectively treated by rehydration therapy. In the majority of cases, oral rehydration therapy is quite satisfactory and has several advantages over intravenous rehydration therapy. Black has recently examined the subject of rehydration therapy and included a list of criteria for assessing the level of dehydration as well as listing accompanying recommendations for therapy.[16] The World Health Organization (WHO) is promoting the widespread use of oral rehydration therapy as a part of their commitment to primary health care.[214] The oral rehydration solution recommended by the WHO can be prepared by adding the following to one liter of water: sodium chloride, 3.5 gm; sodium bicarbonate, 2.5 gm; potassium chloride, 1.5 gm; and glucose, 20 gm.[213] This solution has been used extensively for treatment of enterotoxin-mediated diarrhea and rotaviral diarrhea.[199] Black has discussed this formulation and recommendations for its use.[16] The WHO formulation calls for glucose, but some studies have compared glucose to sucrose as the carbohydrate source. The advantage of sucrose is its lower cost and greater availability. Several groups have reported comparable clinical results when comparing sucrose-containing solutions to glucose-containing solutions.[175] Glucose was slightly superior to sucrose in

a double-blind trial with rotavirus-associated diarrhea in children.[19] Oral rehydration solutions utilizing inexpensive, commonly available ingredients have been described.[75, 132]

Antidiarrheal agents including kaolin-containing adsorbent preparations, pectin suspensions, and intestinal paralytic drugs were of little value in treating acute diarrhea in children.[16, 169] Bismuth subsalicylate (Pepto-Bismol) is somewhat effective in treating travelers' diarrhea.[59]

CONCLUSION

Rotaviruses and Norwalk-like viruses are the two major groups of viruses associated with gastroenteritis. Rotaviral infections are seasonal, occurring mainly in the winter months, and are the major cause of viral gastroenteritis in infants and children. Rotaviral gastroenteritis may lead to severe dehydration. Norwalk-like viruses are a major cause of explosive outbreaks of acute gastroenteritis in older children and adults. These outbreaks are frequently associated with a vehicle such as culinary water, raw vegetables, or raw seafood. Long-term resistance to Norwalk-like viral infections appears to be mediated by non-antibody factors. Several other viral agents have been associated with acute gastroenteritis. The enteric-type adenoviruses may prove to be a third major group of gastroenteritis viruses.

The gastroenteritis viruses are generally fastidious, and thus traditional cell culture isolation and detection procedures are not applicable. Electron microscopy and immune electron microscopy remain among the most powerful techniques for studying these viruses. As viral antigens and antisera become more readily available, more suitable techniques such as ELISA and RIA will be widely available for specific diagnoses of viral gastroenteritis. The in vitro cultivation of these viral agents will facilitate the development of diagnostic reagents and the development and evaluation of vaccines.

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