Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER

32
Enteric Viral Disease

INTRODUCTION

Al Kapikian learned immune electron microscopy from the talented British investigator June Alameda, who had perfected the technique into an art form, as much as a skill. In the early 1970s, Kapikian focused on this approach to the search for the elusive viruses believed to be responsible for nonbacterial gastroenteritis. It was not long before he identified the virions of the so-called Norwalk agent in a diarrheal stool from an adult volunteer who had been challenged with a fecal sample from a child ill during an outbreak of diarrhea. This virus and its soon-to-be-discovered close relatives (the so-called Norwalk-like viruses [NLVs]) proved to be important causes of explosive outbreaks of diarrhea in both children and adults.

NLVs were first reported in 1972 (Kapikian *et al.*, 1972; Kapikian, 1994). Only a year later, Ruth Bishop and her colleagues (1973) found virions of a different size and appearance in cells of the duodenal mucosa of infants with gastroenteritis. These agents proved to be the prototype for a new genus, the rotaviruses (RVs), members of which are infectious for humans and a wide variety of domestic animals. Rotaviruses, classified into Group A, are now recognized to be the major cause of severe diarrheal disease in infants and young children worldwide.

Cholera morbus has plagued and threatened the lives of infants and children since the beginning of recorded history. Morbidity is universal, and the resulting mortality, particularly in developing areas of the world, continues to be tragic. Overall, as many as a third of the deaths in children under the age of 5 in the less-developed countries of the world are attributed to diarrhea. When pathogenic bacteria are excluded, roughly 80% of the episodes of diarrhea (≥3 nonsolid stools per day) are either of unknown etiology or are due to viruses.

With the discovery of the enteroviruses (see Chapter 1) and the demonstration of their chronic presence in the stools of many of those who are infected, it was thought that the search for the cause of nonbacterial diarrhea would soon be over. But despite the presence of high concentrations of enteroviruses in the stools of both ill and healthy children, it shortly became apparent that these viruses were not common etiologic agents of enteritis, but merely nonpathogenic "passengers" in our digestive tracts. Other viruses such as members of many of the common serotypes of the adenoviruses similarly can often be found in the gut, but they too usually fail to cause disease. As an outgrowth of an enormous amount of laboratory work, it was ultimately concluded that the elusive viruses of childhood enteritis are sufficiently fastidious that they cannot be easily grown in tissue culture and in laboratory animals. Thus, in the early 1970s, investigators initiated attempts to identify viral particles in stool extracts using electron microscopy. To accomplish this, the background was stained (so-called negative staining), with the virions in startling contrast, that is, like stars in a dark sky. Should the virions be present in sufficient number, and should their morphology be sufficiently distinctive, infection could be established. By adding specific antibody (or serum from a previously infected patient) to the suspension, the virions would clump with the antibody and an antigenic identification of the virus accomplished. This also proved a means for assaying the relative concentration of antibody in the blood of those who were infected. The technique of negative-staining electron microscopy using clinical enteric specimens is an arduous art form that requires exceptional skill and attention to detail, clearly not a characteristic of many of our species. But, this painstaking approach has now yielded evidence to indicate that viruses of at least six families may contribute to enteric illness in children and in adult citizens

whose immunity has waned (Figure 32.1, Table 32.1). Studies in domestic animals have also shown that diarrheal disease of economic importance is caused by members of these same virus families, possibly by strains of virus that are host-specific. With the development of refined molecular and immunological tools, more sensitive and less laborious diagnostic approaches fortunately are now replacing negative-staining electron microscopy of stool specimens.

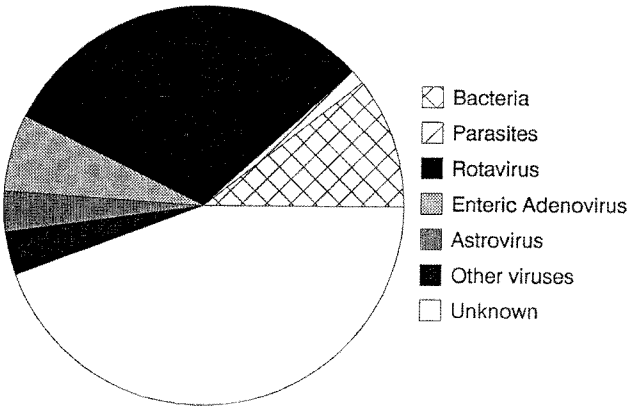

FIGURE 32.1 Estimated median percentage of diarrheal episodes associated with specific viruses and categories of enteropathogens in developed countries. Reprinted with permission from Kapikian (1994).

NORWALK-LIKE VIRUSES (NLVs)

A number of antigenically distinct, nonenveloped, round, 27- to 32-nm RNA viruses classified into a newly proposed genus of the calcivirus family have been found to cause sporadic outbreaks of transient severe enteritis in both children and adults. The etiological role of these viruses as a cause of intestinal disease was established by demonstrating a temporal association of naturally occurring infections (as demonstrated by stool examination using electron microscopy) with illness and by experimental induction of disease in both human volunteers and experimental animals (Hall *et al.*, 1984). The NLVs are provisionally divided for classification purposes into two distinct groups based on genetic analysis (Table 32.2). The relative clinical importance of the viruses of the various groups listed in Table 32.2 has yet to be established, but they are believed to be responsible for a substantial proportion of the nonbacterial outbreaks of acute vomiting and diarrhea that occur in families and institutions.

TABLE 32.1 Enteric Viruses Definitely or Possibly Causing Gastroenteritis in Humans

	Endemic disease	Epidemic outbreaks	Worldwide importance
Rotaviruses			
Group A	+		++++
Groups B and C		+	
Calciviruses			
Norwalk-like viruses		+	
Unclassified	+		
Enteric adenoviruses	+		++
Toroviruses	+		
Astroviruses	+?		+?
Coronaviruses			?

TABLE 32.2 Genotypes of Norwalk-Like Viruses Based on Molecular Analyses

Genotype I
Norwalk[a]
Southampton
Cruise ship
Desert Shield
Genotype II
Gwynedd
Toronto
Lardsdale
Snow Mountain
White River
Hawaii

[a]The geographic name customarily refers to the site where the virus was initially isolated.

Although survey information is incomplete, infections with NLV are thought to occur worldwide. In developing countries. the majority of children are infected during the first 10 years of life (Figure 32.2), whereas in North America infection is relatively uncommon in children, and by the fifth decade of life only 50% of the population possess serological evidence of past infection. It is not clear what proportion of these infections are accompanied by clinical illness, and we possess only limited information on the persistence of serum antibodies during convalescence from infection. Thus, NLV-related disease may occur more commonly than serological surveys of the population now suggest.

Outbreaks of illness develop as a result of a contaminated common source, such as a water supply or food, or as a consequence of person-to-person transmission (Fankhauser *et al.*, 1998). The mean incubation period is approximately 40 hours, and symptoms persist for 12

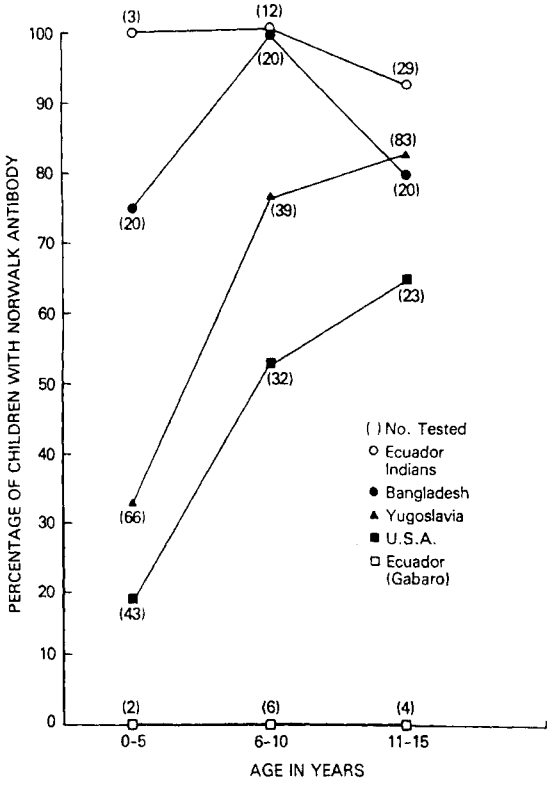

FIGURE 32.2 Age-related prevalence of serum antibodies indicative of past infection by Norwalk virus in various countries. Reprinted with permission from Greenberg *et al.* (1979).

to 24 hours (Table 32.3). The clinical course observed in two volunteers is shown in Figure 32.3) (Dolin *et al.*, 1971).

Volunteer studies have yielded important histological and ultrastructural documentation of the profound but relatively transient changes that occur in the mucosa of the small intestine during the course of infections with NLVs (Agus *et al.*, 1973; Schreiber *et al.*, 1973, 1974; Dolin *et al.*, 1975). Unfortunately, biopsy material from these experimental subjects is, by necessity, limited; thus, the extent and distribution of lesions in the digestive tract is unknown. Of obvious significance is the reduction in the height of the intestinal villi, accompanied by blunting of the villi and evidence of crypt hypertrophy. The individual lining cells of the small intestine exhibit vacuolization of the cytoplasm with loss of polarity. These findings indicate a marked increase in enterocyte replacement as documented by mitotic counts in the epithelium of the crypts. Although cell infiltrates are found in the lamina propria and the core of the villi, inflammation is customarily not a prominent feature of the lesion. Ultrastructurally, the mucosal cells remain intact, but intercellular edema

TABLE 32.3 Symptoms of Norwalk Virus Infections among Children during a Naturally Occurring Outbreak

	Percent
Fever	32
Nausea	85
Vomiting	84
Abdominal cramps	62
Lethargy	57
Diarrhea	44

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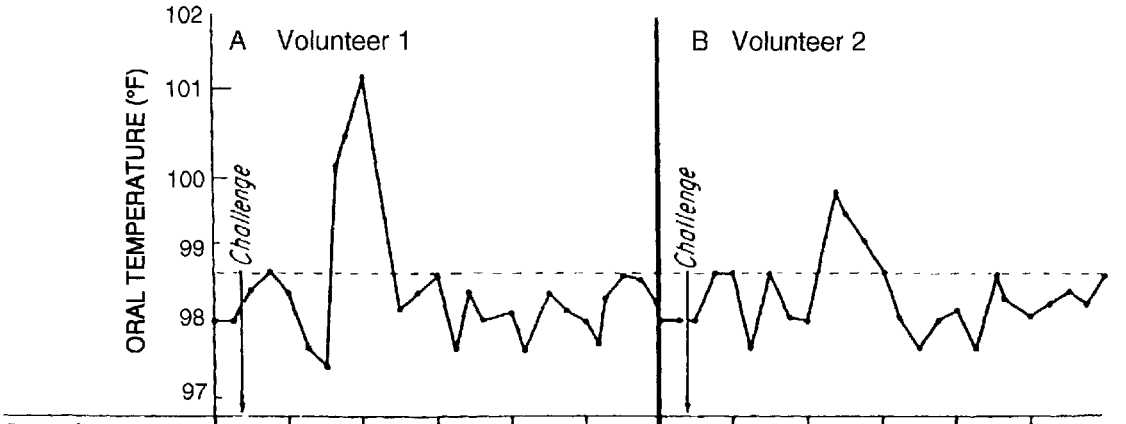
is prominent and the microvilli of the brush border are significantly shortened as shown by electron microscopy. Dilatation of both the endoplasmic reticulum and mitochondria of the mucosal cells is seen, and endocytotic vesicles are evident. Ultrastructural studies thus far have not defined the cell site of replication of the virus, most probably because the virions are relatively small, that is, in a size range that would not readily allow one to distinguish them from ribosomes.

Immunohistochemistry documents a substantial reduction in disaccharides and alkaline phosphatase in the epithelium of the gut. Intestinal biopsies obtained from volunteers 5 to 6 days after the ingestion of NLVs (i.e., 2–4 days after clinical recovery) continue to show shortening of villi and crypt hypertrophy, but the inflammatory response in the lamina propria and submucosa appear to be reduced. At this time, there remains a significant reduction in the surface area of the gut, and a striking increase in mitotic activity of the epithelium is seen.

ROTAVIRUSES (RVs)

RVs are the most important cause of severe and often life-threatening diarrheal disease in infants and young children worldwide (Moulton *et al.*, 1998). Although adults are infected, their symptoms are customarily mild, with asymptomatic infections being common. However, severe infections tend to occur in older persons (Hrdy, 1987; Wenman *et al.*, 1979; Abbas and Denton, 1987; Lewis *et al.*, 1989) and in persons with attenuated immunity (Kaljot *et al.*, 1989; Dryden and Shanson, 1988; Eiden *et al.*, 1985; Wood *et al.*, 1988), but RVs do not appear to be a major contributing factor to the diarrheal disease that so commonly afflicts those with AIDS.

RVs are members of a genus classified in the reovirus family. The Latin *rota* refers to the spoke-wheel



Days after challenge	0	1	2	3	4	5	0	1	2	3	4	5
Diarrhea	0	0	0	0	0	0	0	0	8 stools		0	0
Vomiting	0	20X		0	0	0	0	0	0	0	0	0
Abdominal cramps	0			0	0	0	0	0			0	0
Nausea	0			0	0	0	0	0		0	0	0
Malaise	0			0	0	0	0				0	0
Headache	0			0	0	0	0	0			0	0
Myalgia	0			0	0	0	0	0		0	0	0
Anorexia	0				0	0	0				0	0
WBC	8,400	18,450	16,600	14,100	11,200	-	8,200	8,100	8,700	8,200	8,300	-

FIGURE 32.3 Response of two volunteers to oral administration of Norwalk virus. The height of the curve is directly proportional to the severity of the sign or symptom. Volunteer 1 had severe vomiting without diarrhea, and volunteer 2 had diarrhea without vomiting, although both received the same inoculum. Reprinted with permission from Dolin *et al.* (1971).

appearance of these nonenveloped 70-nm RNA virions in negatively stained electron micrographs. Based on antigenic analysis of the virion coat proteins, five groups (A–E) have been established. The majority of human infections are due to viruses of group A in regions of the world where intensive studies have thus far been conducted. Overall, the prevalence of group B and C infections is low, and they appear only sporadically in developed countries. Widespread epidemics of group B viruses have been reported from the People's Republic of China; however, overall, infection by group B and C viruses in China as measured by presence of antibodies in the blood serum of members of the general population remains low, that is, ~10% (Qui *et al.*, 1986).

Because these viruses are highly mutable, stool specimens from individuals may yield a diversity of variants that differ one from another on the basis of minor changes in the amino-acid makeup of the virion coat protein. The relative pathogenicity of these genetically diverse agents is unknown. Although RVs from domestic animals have been shown experimentally to infect children, there is little evidence to indicate that animals are a significant reservoir for human infections.

In developed countries, RV infections typically occur between the ages of 6 and 24 months. In one study conducted in North America, 40% of children were infected with at least one strain of RV during the first year of life (Ward and Bernstein, 1994) (Figure 32.4). However, fewer than a third of these infections were symptomatic (Wenman *et al.*, 1979). In developing countries and in persons residing under poor socioeconomic conditions, as many as 30% of children are infected by 6 months of age (Moulton *et al.*, 1998), and many infants experience their first encounter with RVs in the newborn nursery during the first week of life (Bishop, 1994). This high prevalence of infection during early life doubtlessly represents both the common occurrence of RV infections in persons residing in these environments (thus facilitating person-to-person spread) and the lack of acquired secretory IgA to the virus in the gut.

The clinical features of RV infections — fever, vomiting and diarrhea — are known to all mothers. Yet,

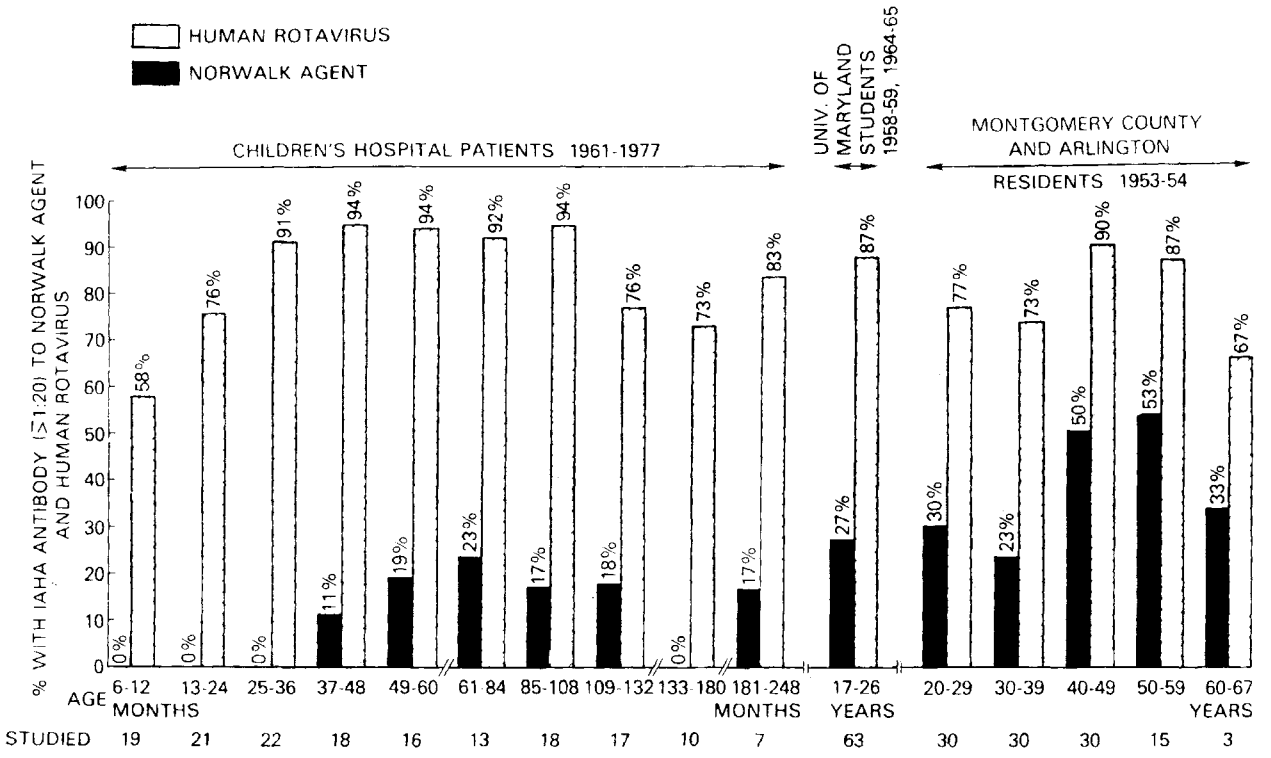


FIGURE 32.4 Prevalence of antibody to rotaviruses and Norwalk virus by age utilizing three different study populations near Washington, DC. Note the evidence of infection with rotavirus early in life, and their persistence throughout adulthood. In comparison, the Norwalk virus infections occur later in life, and a much smaller proportion of the population shows evidence of past infection. Reprinted with permission from Kapikian (1994).

because symptoms usually are mercifully short-lived (24 to 48 hr), the maintenance of fluid and electrolyte balance is rarely a problem in otherwise healthy infants (Table 32.4). In developing countries, however, the threat to life is more imposing, particularly since infections so frequently occur among the very young.

Illness in adults is less severe (Table 32.5), if it occurs at all. Indeed, 60 to 80% of infections in adults are asymptomatic. This may reflect age-related resistance (as documented in animals) (Ciarlet *et al.*, 1998) or the acquisition of a spectrum of serotype-specific IgA antibodies in the gut resulting from previous natural infection. As the years pass, immunity may wane among the elderly, in part due to less frequent encounters with the virus in their home setting. Older folks more often develop severe diarrheal illnesses when infected with RVs, and deaths are reported (Hrdy, 1987).

RVs appear to replicate exclusively in the mucosal lining cells of the villi of the small intestine and not elsewhere in the gut (Figures 32.5 and 32.6). Up to 10^{10} virions can be found in a gram of feces during the acute illness! This extraordinarily high concentration of virus in diarrheal stools no doubt accounts in part for the ease of transmissibility of these viruses among close contacts. Since the virions are also relatively resistant to environmental stresses, they can persist in water supplies and food. Infection occurs exclusively by the oral route.

As might be expected, relatively few morphologic studies have been carried out on enteric biopsies from infants and children with documented RV infections. Davidson and Barnes (1979) examined duodenal biopsies obtained 24 to 120 hours after the onset of symptoms from children 2 to 33 months of age. Abnormalities were found in 40% of the biopsies. There was blunting of villi, along with an increase in crypt depth and flattening of the epithelial cells lining the villi. Inflammatory cells were present in the lamina propria in 2 of the 17 infants studied. The pathological changes were said to resemble those seen in celiac disease with loss of villi, prominent crypt hypertrophy, and an infiltrate of inflammatory cells. RV particles were found in the enterocytes of these patients by electron microscopy. Histochemical evaluation of the gut mucosa

TABLE 32.4 Clinical Features of Children under Age 15 with Rotavirus Infections

	Percentage of hospitalized	Percentage of nonhospitalized
Diarrhea	94	100
Diarrhea (>10 stools/day)	28	17
Vomiting	92	83
Vomiting (>5 ×/day)	51[a]	28
Fever	86	83
Temperature >39°C	35	47
Respiratory symptoms	32	34
Dehydration	72[a]	30

Reprinted with permission from Uhnoo *et al.* (1986).

[a]Statistically significant ($p > 0.05$) difference between hospitalized and nonhospitalized patients.

TABLE 32.5 Symptoms in North American Adults with Familially Acquired Rotavirus Infections

Symptoms	Percent
Diarrhea	32
Abdominal cramps	24
Vomiting	10
Respiratory	7
Fever	6

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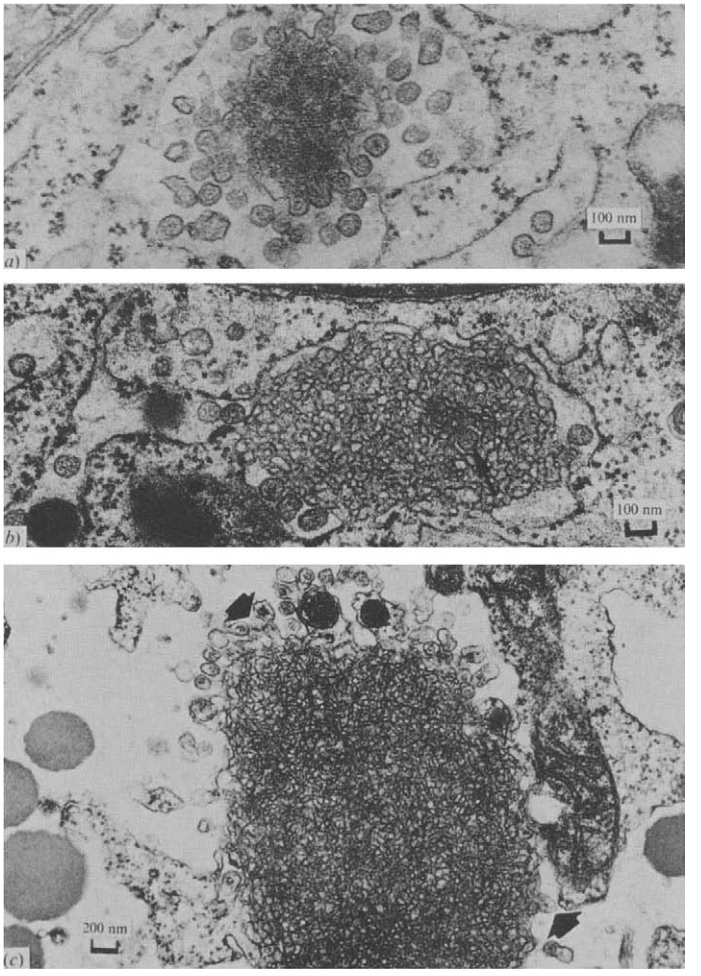

FIGURE 32.5 Experimentally induced rotavirus infection in gnotobiotic piglets. Villous epithelium in the top panel shows a viroplasm with viral particles budding into the distended cisternae of endoplasmic reticulum. In the middle panel, enveloped virus particles are situated within (arrow) and at the edge of convoluted smooth membrane. The bottom panel displays the fine structural features of the viroplasm shown in Figure 32.6. Reprinted with permission from Saif *et al.* (1978).

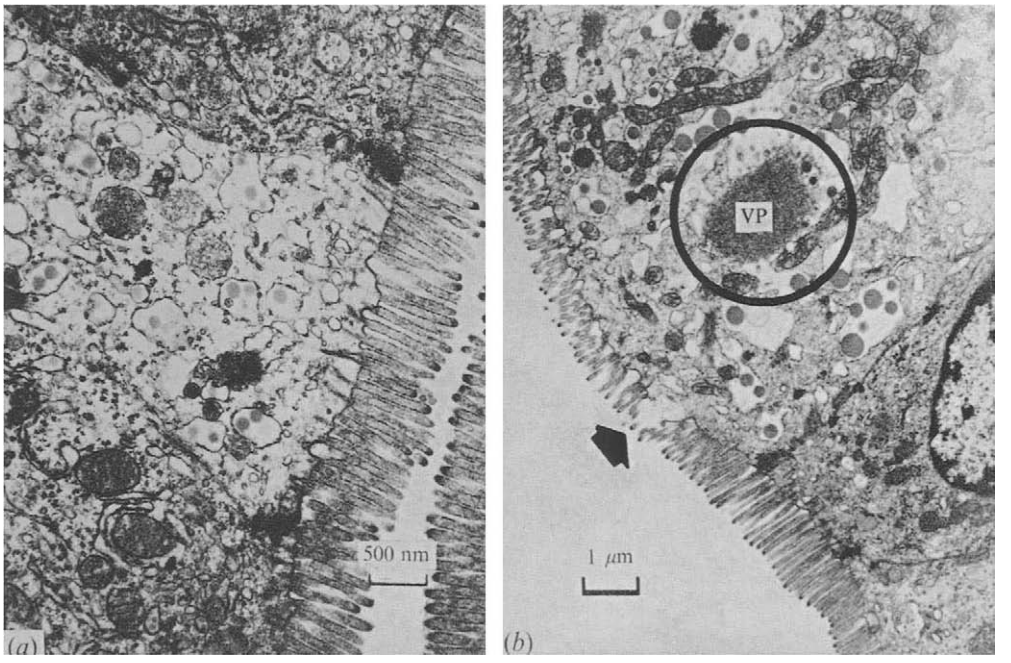

FIGURE 32.6 Experimentally induced rotavirus infection in gnotobiotic piglets. Electron micrographs of villous epithelium. Note distended cisternae of the rough endoplasmic reticulum and rarefaction of cytoplasm in panel **A**. The affected cell is situated between two seemingly normal cells. Panel **B** shows cells with shortened irregular microvilli and a break in the viroplasm–VP border (arrow) (see Figure 32.5). Reprinted with permission from Saif *et al.* (1978).

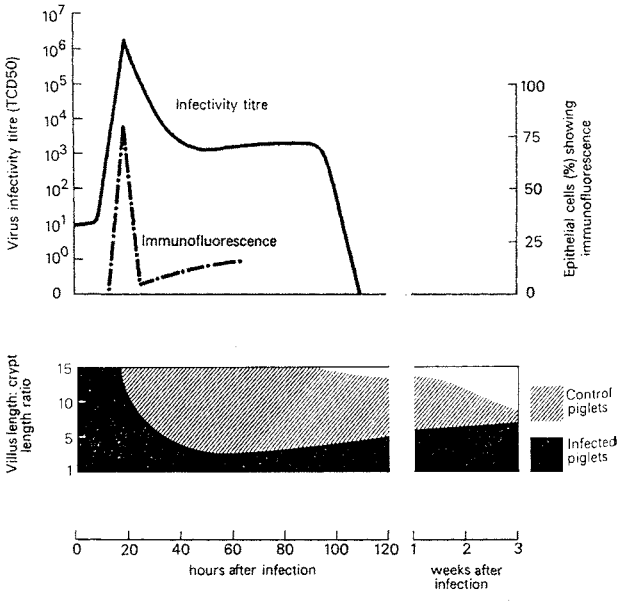

FIGURE 32.7 Experimentally induced rotavirus infections in gnotobiotic piglets. Temporal evidence of infectivity as based on assays of bowel content and immunofluorescence of mucosal lining cells for the presence of virus. The associated changes in the villus length:crypt length ratio is shown for infected (solid black) and control (broken line) animals. Note the protracted recovery time. Reprinted with permission from Crouch and Woode (1978).

showed that disaccharidase concentrations were reduced in the epithelium. Repeat biopsies were done on several children during convalescence (3 to 8 weeks), and regeneration of the mucosa was found.

As noted above, a wide variety of wild and domesticated mammals and poultry (Domermuth and Gross, 1985) acquire RV infections naturally. Experimental studies in calves (Reynolds *et al.*, 1985), lambs (Snodgrass *et al.*, 1977, 1979), and piglets (Theil *et al.*, 1978; Crouch and Woode, 1978) have provided insight into the location of viral replication in the gut and the associated histologic changes (Figure 32.7). To a large extent, the changes observed in children (Davidson and Barnes, 1979) were found in these animals. In calves, the lesions tended to be more prominent in the proximal small intestine, whereas in lambs the distal ileum was more severely affected. Table 32.6 summarizes the results of immunohistochemical studies that document viral replication in the gut of lambs after experimental infection *per os*. In general, the sites of RV replication correlate with the pathological changes found in the intestinal mucosa (Snodgrass *et al.*, 1977). As might be expected, the concentrations of virus in the gut of these piglets were highest before lesions in the mucosa appeared (Crouch and Woode, 1978).

TABLE 32.6 Immunofluorescent Staining of the Intestine of an Experimentally Infected Lamb for Rotavirus Antigen

Time killed (hours p.i.)	Small intestine			Large intestine	
	Anterior	Middle	Posterior	Colon	Caecum
12	–	++++	++++	–	–
18	++	+++	+++	++	++
27	–	++	++	+	++
42	+	+	–	–	++
48	–	+	+	+	–
72	++	–	–	–	–
96	+	+	+	–	+
144	–	–	–	–	–
Control	–	–	–	–	–
Control	–	–	–	–	–

Reprinted with permission from Snodgrass *et al.* (1977).

++++ = Continuous fluorescent epithelial cells present over at least distal half of the villi. +++ = Continuous fluorescent epithelial cells present over tip or distal third of the villi. ++ = Sporadic fluorescent epithelial cells present in most villi. + = Sporadic fluorescent epithelial cells present in a few villi.

FIGURE 32.8 Photomicrographs of histological cross-sections from the small intestines of two piglets. (**Top**) Observe the long slender villi with lightly stained epithelium that dominate the mucosa in the normal animal. There is a narrow band of crypts with a darkly stained epithelium around the base of the mucosa. (**Bottom**) Severe villous atrophy caused by the swine coronavirus responsible for transmissible gastroenteritis. Reprinted with permission from Moon (1994).

ADDITIONAL ENTERIC VIRUSES

Viruses of several additional families have been implicated in human enteritis, but, in general, the disease is relatively mild and not life threatening (Table 32.1). Information concerned with the pathological effects of these viruses on the gut mucosa is lacking. In many studies, the common occurrence of asymptomatic enteric infections often makes it difficult to establish, on epidemiological grounds, an etiological relationship between the infection and disease; yet, under certain circumstances, these viruses may be pathogenic for humans.

The enteric adenoviruses types 40 and 41 are recognized causes of enteritis, but they account for fewer than 10% of cases (see Chapter 14) (Brandt *et al.*, 1985). In two recent studies, toroviruses were associated with enteritis manifest in children as both vomiting and diarrhea. Although not severe, the stools commonly were bloody and disease persisted for several days (Koopmans *et al.*, 1997). Enteritis due to toroviruses also occurs in cattle and horses (Weiss and Horzinek, 1987; Woode *et al.*, 1982; Jamieson *et al.*, 1998). Astroviruses and coronaviruses have been implicated as causes of diarrheal disease in humans, but the evidence supporting a cause-and-effect association is weak (Phillips *et al.*, 1982; Lew *et al.*, 1990). These latter viruses are etiologically responsible for disease in young domestic animals (Mebus *et al.*, 1973; Thake *et al.*, 1973; Gray *et al.*, 1980; Kurtz *et al.*, 1979) (Figures 32.8 and 32.9).

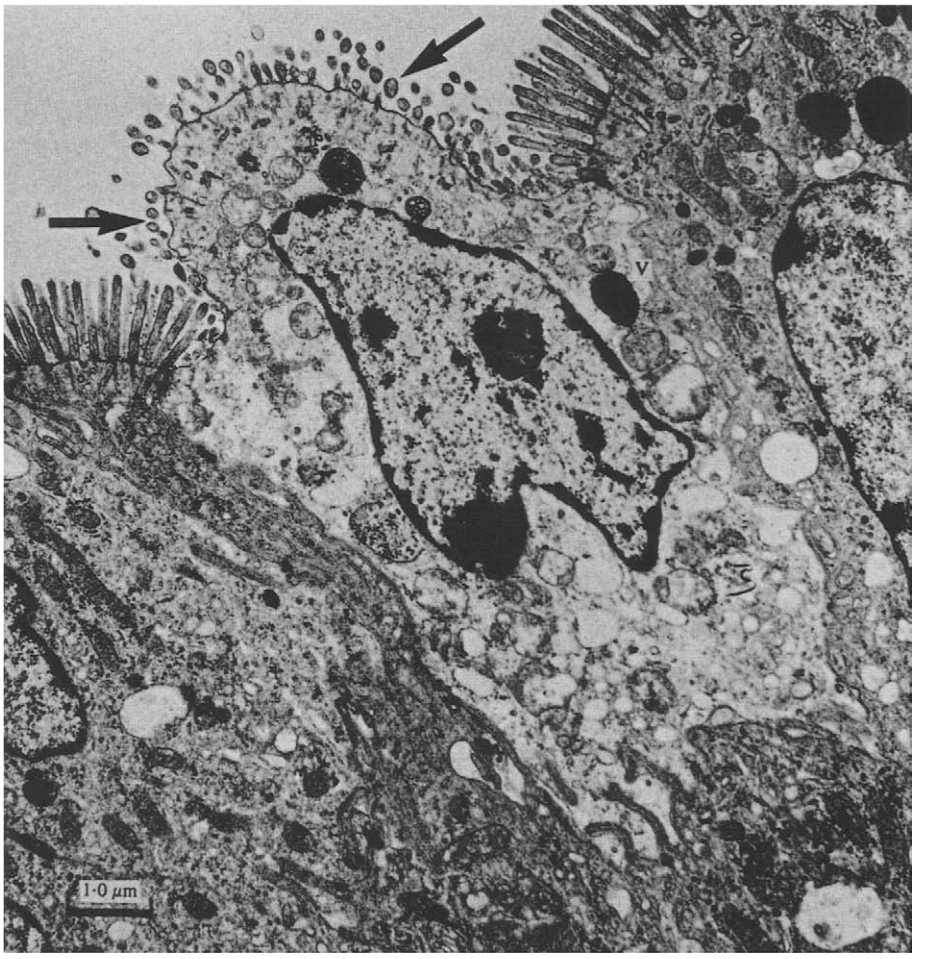

FIGURE 32.9 Degeneration of mucosal lining cell in the midgut of a lamb infected with an astrovirus. Note the changes in the microvilli (arrows) and virions in a lysosome (V). Reprinted with permission from Gray *et al.* (1980).

PATHOPHYSIOLOGY OF VIRAL ENTERITIS

Pathological observations provide insight into the physiological basis for enteritis in those infected with enteropathic viruses. At present, relatively few clinical studies have addressed these issues in detail. Involvement of the upper intestinal tract (duodenum and jejunum) may account for the vomiting that so frequently occurs in NLV infections. Diarrheal disease no doubt is consequent to the profound changes in the intestinal mucosa that occur during the acute illness. Reduction in the surface area of the gut mucosa and functional alterations in the individual enterocytes that line villi reduce absorption of fluids and solids beyond the capacity of the colon to compensate. The loss of disaccharidases in the mucosal cells of the small intestine increases the carbohydrate concentrations of the large bowel content, resulting in the generation of fermentation products.

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