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NEW JDDR SECTION

In this issue of the "Journal of Diarrhoeal Diseases Research," we are introducing a new element, "Editorial Perspectives." Appearing from time to time, this section will present, in the context of a brief review of a given subject, the author's thoughts.

This month, as we near the winter season when rotavirus becomes prominent, Dr. Thomas C. Butler has focussed on viral diarrhoeas, from the Asian viewpoint. The article originally was presented as a paper, in November, 1982, at the Annual Convention of the Philippine Society of Microbiology and Infectious Diseases.

We shall be interested in our readers' reactions to this new section, and welcome contributions to it. In this way, we hope to explore different perspectives, as well as to offer opinions on controversial subjects.

W.B. Greenough, III
Editor-in-Chief

EDITORIAL PERSPECTIVE

VIRAL DIARRHOEAS

To place viral diarrhoeas in perspective, it is useful to consider the worldwide incidence of these diseases. Because they are very common or have high case fatality ratios, several major infectious diseases have attracted priority for investigation and prevention. Thus, in a worldwide estimate in 1979 of incidence and mortality for several infectious diseases, Walsh and Warren (1) found diarrhoeas and respiratory infections to be the most prevalent (Table I). Annual deaths were estimated at 5-10 million for diarrhoeas and 4-5 million for respiratory infections. And while malaria was pinpointed as the single biggest killer (1.2 million) disease, rotavirus diarrhoea was estimated to be number two (500,000 deaths). Moreover, with an estimated 500 million cases annually, rotavirus accounts for 10 percent of all diarrhoea cases. It is apparent, then, that the viral diarrhoeas deserve attention as a leading cause of morbidity and mortality in the world today.

TABLE I – INCIDENCE AND FATALITY OF DIARRHOEAL DISEASES WORLDWIDE IN RELATION TO CERTAIN OTHER INFECTIOUS DISEASES*

	No. of Cases Annually	No. of Deaths Annually
Diarrhoeas	3-5 billion	5-10 million
Respiratory diseases	Not estimated	4-5 million
Malaria	150 million	1.2 million
Tuberculosis	7,000,000	400,000
Amebiasis	1,500,000	30,000
Typhoid fever	500,000	25,000
Giardiasis	500,000	Very low
Rotavirus diarrhoea	500 million	500,000

*Adapted from estimates, as compiled by Walsh and Warren (1)

Although many viruses inhabit the human intestinal tract, the two most important diarrhoeal pathogens are rotavirus and Norwalk virus. The former first was detected in Australian diarrhoeal children by Bishop *et al.* (2), using electron microscopy of duodenal biopsies. Other viruses, such as astroviruses and intestinal adenoviruses, also are diarrhoeal pathogens. Some characteristics of these viruses appear in Table II. Rotavirus belongs to the Reoviridiae family. They are 70 nm in diameter, and can be detected by enzyme-linked immunosorbent assay (ELISA). Norwalk virus probably is a calicivirus. It is smaller (about 27 nm) and has been detected in stool by immune electron microscopy. Earlier, the Norwalk agent was thought to be a parvovirus, but a single structural protein composition makes calicivirus more likely.

The rotavirus nucleic acid is known to be RNA, with 11 double-stranded segments. While the nucleic acid type of Norwalk virus is unknown, it too is likely to be RNA, because other caliciviruses contain RNA. Rotavirus has an outer capsid protein

TABLE II – CHARACTERISTICS OF VIRUSES CAUSING GASTROENTERITIS

Feature	Rotavirus	Norwalk Virus
Family	Reoviridiae	Calicivirus
Size	70 nm	27 nm
Detection	ELISA	Immune electron microscopy
Nucleic acid	RNA 11 segments double-stranded	Unknown
Structural protein	Outer capsid with 3-5 polypeptides. Inner capsid with 41,000–128,000 MW	MW 59,000
Soluble protein	RNA polymerase	MW 30,000

coat comprised of 3-5 polypeptides; and an inner capsid protein with a molecular weight (MW) of 41-128,000 daltons. Rotavirus contains an enzyme RNA polymerase. Norwalk virus has one structural protein of MW 59,000 daltons and a soluble protein of MW 30,000 daltons (3,4).

"Rotavirus" means "wheel," and derives from structural protein units which radiate outwards, like spokes. "Norwalk" virus is named for an Ohio (USA) town, where this agent first was described in 1968, as a cause of winter vomiting disease.

Both agents occur worldwide, and cause disease predominantly in children. Thus, for rotavirus, while adults can become infected, a prospective Canadian family study (5) showed that the adult infection rate was about half that of children. As for Norwalk virus, adults have become afflicted during Norwalk-caused diarrhoea outbreaks. Some comparative epidemiological features appear in Table III. Significantly, the major rotavirus reservoir is believed to exist in asymptomatic adults. The reason: children commonly get rotavirus diarrhoea, while adults often carry the virus without symptoms. In a Canadian study, Gurwith *et al.* (6) showed that in one-child families, children had a higher rotavirus attack rate than did children with siblings, suggesting that children acquire infection from their parents or other adults. Moreover, rotavirus can be spread within hospitals or other environments. Thus, an outbreak of type 2 rotavirus infection was described in a children's play group, in which all children developed disease, as well as most of their parents (7). Similarly, Norwalk virus has caused disease outbreaks in such well-defined populations as camps, ships, schools and nursing homes. Food and water as transmission vehicles have been suggested by epidemiologic evidence; and inadequate sanitation has been identified as a Norwalk virus transmission risk factor (8, 9).

While they occur year-round, rotavirus infections predominate in the winter. This is particularly true in temperate countries, though a similar pattern has been shown in tropical areas. Norwalk virus infections also occur in winter, but are more likely than rotavirus to be evenly distributed during the year. Rotavirus also may be an important cause of traveller's diarrhoea, as shown in a study of travellers in Mexico and Honduras, who experienced diarrhoea and four-fold or greater antibody titer increases against rotavirus antigen (10).

Acquisition of antibodies against these viruses in Bangladeshi children was followed prospectively for 1 year, with periodic sampling of blood by Black *et al.* (11). Antibody incidence increased in children aged 2 months to 4 years, and was higher for rotavirus than for Norwalk virus in all age groups. The peak age for rotavirus acquisition was 1-2 years, but continued through age 4. Acquisition of antibody to Norwalk also was highest for this age group, but declined sharply by age 4.

As antiviral antibody prevalence rises with age, nearly all older children will have been exposed to Norwalk virus. In general, adults have serum antibodies against both viruses, but the titers decline somewhat with age.

These antibodies do not necessarily protect against reinfection. Thus, when exposed to rota-

TABLE III – CONTRASTING EPIDEMIOLOGICAL FEATURES OF ROTAVIRUS AND NORWALK VIRUS GASTROENTERITIS

	Rotavirus	Norwalk Virus
Ages:	Children 0-4 years Occasionally adults	Children, also adults
Places:	Endemic throughout world; nosocomial spread; asymptomatic adult carriers with infection reservoir	Endemic throughout world; outbreaks in camps, ships, schools, & nursing homes associated with water or food
Season:	Mainly winter	All seasons.

viruses, persons with antibodies are just as likely

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other than stool. Older children and adults are less likely than children to have severe disease, including vomiting and respiratory symptoms.

TABLE IV – CLINICAL FEATURES OF ROTAVIRUS INFECTION CONTRASTED WITH GASTROENTERITIS FROM OTHER CAUSES. FIGURES ARE THE PERCENT OF CASES WITH SYMPTOMS

	Patients with Rotavirus (%)	Patients without Rotavirus (%)
Diarrhoea	100	100
Vomiting	96	58†
Fever	77	61
Dehydration	83	40†
Irritability	47	40
Pharyngeal erythema	49	32
Rhinitis	26	22
Otitis media	19	9
Cervical lymph nodes	18	9

*Adapted from Kapikian *et al.* (3)
†Vomiting and dehydration significantly more frequent in rotavirus cases.

The stools of patients with virus diarrhoea usually are liquid or semi-solid, and often contain undigested milk or mucus. The stools rarely have gross blood. Fecal leukocytes usually are absent but Clemens *et al.* (13) recently demonstrated that some children in Bangladesh with rotavirus infection had increased stool leukocytes and blood.

The precise rotavirus diarrhoea mechanism is unknown, but the following has been proposed:

1. Virus particles infect epithelial cells, especially those of villi. The virus particles replicate only within the epithelial cells.
2. Morphological changes occur, including decreases in brush border surface, and height of columnar cells and villis.
3. Infected epithelial cells die faster than usual, causing faster migration of crypt cells up to the villi.
4. The new villus cells are not differentiated for absorption, and actually are programed to secrete like normal crypt cells.

The evidence for this mechanism is as follows: biopsies from human rotavirus infection show the intracellular infection and morphological changes in cells. In experimental viral diarrhoea studies in piglets infected by a corona virus or with human rotavirus, small intestinal absorption shows such a pattern (14,15).

Some differences between rotavirus and cholera diarrhoea have been demonstrated. Cholera stool has a high sodium concentration (about 100 meq/L or more), whereas rotavirus stool shows a sodium concentration of about 40 meq/L. Cholera produces acidosis by loss to stool of about 40-50 mmol/L bicarbonate, while rotavirus stool contains only about 6 mmol/L (16). These stool composition differences and the fact that rotavirus infection almost never produces the very high purging rates of cholera indicate that different pathophysiologies are operating in these two distinct diseases. One basic difference between cholera and rotavirus has been revealed by Davidson *et al.* (15) in piglets infected with human rotavirus. The enterocytes of jejunal villi in the piglets did not show elevated levels of cyclic AMP, as would have been expected in an enterotoxin-mediated disease of the small intestine.

Rotavirus diarrhoea is treated primarily by rehydration. The virus infection is self-limited and requires no other therapy. However, while the standard WHO oral rehydration solution (ORS) has been shown empirically to work well (17), the glucose was not absorbed as well as in diarrhoeal diseases caused by other pathogens.

This was shown by Nalin et al (17), in studies of children in Costa Rica who frequently had high stool glucose levels (about 27.8 mmol/L) during ORS treatment. This finding is consistent with experiments by Davidson *et al.* (15), showing that in rotavirus-infected piglets there is a defect in glucose-coupled sodium transport. The ability of ORS to rehydrate children with viral diarrhoea in the face of this glucose absorption defect, suggests that these patients have a lesser demand for glucose-facilitated sodium absorption than do heavily purging cholera cases. This observation would be compatible with the clinical experience that, compared to cholera, rotavirus diarrhoea usually is milder, with less loss of sodium and water.

There are two immunological approaches to preventing rotavirus infection which may become future therapeutic and vaccine strategies: give passive immunity to high risk children; and/or give active immunity, using live oral vaccines. Barnes and co-workers in Australia did a study, in which human gammaglobulin was given orally to premature babies, who are at high risk of developing rotavirus diarrhoea in the first weeks of life (18). Two groups were randomly assigned to receive orally gammaglobulin or a placebo. Then the babies who excreted rotavirus and had diarrhoea were compared. Both groups had diarrhoea and virus excretion with about the same frequency. However, the gammaglobulin group excreted virus later, more often in the second week, whereas the placebo group excreted it during the first week. Diarrhoea severity was greater in the placebo group, and many infants had to go on a lactose-free feeding regimen to correct the clinical condition. This experiment confirms in humans what is known from animal experiments. For example, newborn calves were fed antibody containing colostrum 4 h before and 4 and 24 h after rotavirus challenge. They were protected against infection. In other experiments, lambs were fed antibody containing colostrum on the first day of life and were challenged the next day. They were not protected. Daily feeding of colostrum did protect them. Thus, antibody had to be present in the intestinal lumen at the time of virus challenge in order to be protective (19).

The prospects for rotavirus vaccines are favorable. Kapikian *et al.* (19) have developed a vaccine, an orally administered live attenuated virus which carries antigens of both human virus types. Because human rotavirus could not be grown in tissue culture, it was necessary to modify the virus. This was done by passaging a human virus strain 11 times through germ-free piglets. Then the virus was able to grow in tissue culture containing African green monkey kidney cells. In another approach, called genetic reassortment, human rotavirus is cultivated with a calf rotavirus, which can be propagated. After incubation, viruses multiply which contain genes and, consequently, antigens of both viruses. This is possible, because rotavirus has a segmented RNA genome which can exchange segments with other closely-related viruses.

Still another approach to vaccine development uses an attenuated bovine rotavirus strain antigenically related to human rotavirus. Vesikari *et al.* (20) gave the vaccine orally to Finnish adults and children. High rates of seroconversion suggested that this too is a promising vaccine candidate.

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