DIARRHŒA AND VOMITING IN INFANCY AND CHILDHOOD: VIRAL STUDIES*

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THE POSSIBILITY of a viral etiology for the self-limited episodes of diarrhœa and vomiting in children, as well as in adults, has been postulated for a long time. Until a few years ago, there was no evidence to support this assumption.

With the introduction of tissue culture methods in virus research, many workers were soon able to establish a link between certain viruses and outbreaks of diarrhœa and vomiting occurring sporadically or in small epidemics. The present work offers the results of viral studies carried out on infants and children seen in hospital with this syndrome from July 1958 to May 1959.

Among the most valuable contributions in this field of research, Eichenwald *et al.*,[1] in 1958, clearly established the causal relationship of ECHO type 18 with an outbreak of diarrhœa in premature and newborn babies at the Cornell University Medical Center in New York. Ramos-Alvarez and Sabin,[2] in 1958, reported their findings on a series of cases collected throughout two consecutive summers and stressed the importance of the ECHO viruses as a cause of diarrhœa; they also mentioned the possible significance of adenoviruses in this regard, having found three of such viruses in the test group (using only monkey kidney tissue cultures) as compared with none in the control group.

A report of great interest (for purposes of comparison) appeared in the British literature in December 1958. Sommerville,[3] in a one-year survey, found 75 enteroviruses in 338 rectal swabs from children with diarrhœa (an average of 22%), and 17 in a control group of 115 children with respiratory infections. The incidence of polio and Coxsackie viruses in the two groups was comparable, but the proportion of ECHO viruses was greater in the test group, although the difference was not statistically significant. The presence of only one adenovirus was mentioned. Up to now, from the previous reports and reports from other workers, it appears that ECHO viruses (2, 7, 8, 10, 11, 12, 14, 18, 19, 20) have been associated with acute episodes of diarrhœa and vomiting.

Finally, in adults a filtrable agent, which cannot be isolated on tissue cultures, has been shown to cause diarrhœa in several successive volunteers on whom stool filtrates were used, and to induce immunity.[4] One strain is called "F.S."[5] because of the presence of fever in the clinical picture, the other the "Marcy strain",[6] from an afebrile form of non-bacterial gastroenteritis. There are no comparable studies in children.

MATERIAL AND METHODS

From July 1958 to May 1959, rectal swabs were obtained from 74 children with diarrhœa and vomiting and from 62 controls in the Montreal Children's Hospital. In the diarrhœa group, blood specimens were also taken during the acute and convalescent phase. The rectal swabs chosen were all negative for a bacterial pathogen (Shigella, Salmonella and pathogenic coliforms). Cases of diarrhœa in which a cause other than viral could be suspected were also eliminated, i.e. diarrhœa accompanying parenteral infections known to produce diarrhœa (mastoiditis in infants for example), malabsorption syndromes, chemical intoxications, food poisoning, etc.

The case accepted for study was one of diarrhœa and vomiting as the major complaint, with or without fever, and/or symptoms of upper respiratory infection; the course of illness was usually one week or less. Most of these cases were in-patients; only eight swabs were taken in the outdoor department of the hospital. The control swabs were obtained in another so-called "clean ward" from patients admitted recently for investigation of some chronic problem; occasionally, owing to temporary shortage of these patients, ones with pneumonia were used. A few controls were taken at the outdoor department. These controls were matched for age and time of sampling. The history and physical examination as well as the white blood cell and differential counts were noted in each instance.

The rectal swabs were processed according to the method of Alvarez and Sabin.[2] The rectal swabs used were the same as for the bacteriology department of the hospital. Immediately after sampling the swabs were stored for a maximum period of 48 hours in the freezer compartment of an ordinary refrigerator. They were then collected and transferred to the freezer of the Institute of Microbiology at -20° F., with 5 c.c. of Hank's solution added. On the day of the test the samples were thawed slowly at refrigerator temperature or more rapidly in cold water; 0.5 c.c. of an antibiotic solution was added in order to yield concentrations of 2000 units of penicillin per c.c., 2 mg. of streptomycin per c.c. and 150 units of nystatin (Mycostatin) per c.c. The pH was then brought to 8 by use of sodium bicarbonate 4.4% solution. After a storage period of 30 minutes in the refrigerator, six or eight tubes of tissue cultures (equal number of HeLa and monkey kidney) were inoculated with 0.5 c.c. of material each. The matched control cases were inoculated the same day on the same lot of tubes. At least two passages were made, the average number of passages being four. In order to detect, on occasion, a cytopathogenic agent originating from the tissue culture itself, serial passage of the non-inoculated control tubes was

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TABLE I.—VIRUS ISOLATION IN RECTAL SWABS

Cases of diarrhœa and vomiting

Adeno type	III	III	I	I	V	V	V	VII		
Polio type	I	III								
Coxsackie type	B_5								14/74 children	
ECHO type	10	22								
Unidentified	(1)									
	1	2	3	4	5	6	7	8	9	10

Number of cases

Controls

Adeno type	I	I	VII					
Polio type								
Coxsackie type	B_5							5/62 children
ECHO type	9							
Unidentified	0							
	1	2	3	4	5	6	7	8

Number of cases

also done. However, we could never reproduce in subcultures any cytopathogenic effect present in both non-inoculated and inoculated cultures at the same time. The antibiotic-resistant samples that became contaminated were mixed with ether, allowed to evaporate and reinoculated.

Each cytopathogenic agent recovered from monkey-kidney tissue-cultures was typed against polio, Coxsackie, and ECHO antisera. Pools were used for the preliminary identification: polio I, II and III together, Cox. A_9, $B_{1, 2, 4}$, Cox. B_3, B_5, five pools of ECHO: 6-9-16, 8-10-18, 2-3-5-7, 11-12-14-19, 1-13-15-17, and ECHO type 22. Most of the antisera were obtained from Microbiological Associates, Bethesda, Maryland. Some of the Coxsackie antisera and ECHO type 22 had been prepared and standardized in our laboratory. The agent was finally typed by neutralization tests with the individual antisera. In addition, whenever one or two sera (acute and convalescent) were available in these cases, a neutralization test using the standard laboratory virus was carried out; no neutralization tests were done in cases where no viruses could be recovered from the rectal swab.

When a cytopathogenic agent was isolated on HeLa tissue cultures, a preliminary screening test was performed. The agent recovered was used as antigen in a complement-fixation test for adenoviruses with a known positive serum. If positive, this agent was typed with the available adenovirus antisera 1 to 7. The two-phase sera were also used, when available, for complement-fixation tests for influenza and adenovirus.

RESULTS AND COMMENTS

Among the 74 cases of diarrhœa a virus was recovered from the rectal swab in 14 cases, which represents an isolation rate of 19%. In the control group of 62 cases a virus was isolated in five cases, an average of 8%; more than half of the viruses in the diarrhœa group, as well as in the control group, were adenoviruses; the type of adenoviruses recovered varied in epidemic fashion throughout the year and followed the overall pattern of adenovirus isolation in our laboratory.

In addition, out of a total of 28 complement-fixation tests (paired) done for adenoviruses, at least seven showed a significant rising titre (see Table II). In five of these cases, no adenoviruses could be recovered from the rectal swab. The fourfold increase in antibodies is highly significant in these cases despite a negative rectal swab, which can be explained by one of several reasons. The number of positive results may thus be brought to 19 instead of 14 in the diarrhœa group, although this cannot be compared with the control group where no complement-fixation tests were performed. The two phase sera necessary to show a similar rise in antibodies in cases where a virus was found in the rectal swab were available in only six of the 18 cases; five of these six cases had a rise in antibodies by complement-fixation or neutralization test (Table II).

One patient, L.G. (see Table II), showed no rise in titre as opposed to the others; unlike most of the other cases in this series (95%), this patient had not been admitted for diarrhœa and vomiting, but had developed this while in hospital with pneumonia. It is reasonable to assume, in this case, that an adenovirus respiratory infection originally was followed by a secondary bacterial infection, for which the child was admitted; the adenovirus remained in the stool but the level of complement-fixing antibodies had fallen in the meantime (or else failed to rise at all); the episode of diarrhœa remains unexplained in this case. This example further emphasizes the diagnostic value of a demonstrable rise in antibodies over the mere finding of an adenovirus in the stool.

Table III summarizes the clinical course in seven cases of adenovirus infection. The infection with these viruses gave rise to diarrhœa and vomiting alone, or in combination with symptoms of respiratory infection.

As far as one can conclude from such a limited number of cases, it appears that respiratory symptoms are a part of the picture mostly in older children as compared with the infant or young child who shows the simpler picture of diarrhœa and vomiting.

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TABLE II.—DATA ON CASES WITH POSITIVE RESULTS IN CHRONOLOGICAL ORDER

Group	Name	Age	1st day of illness	Day rectal swab taken	Type of virus isolated	Antibodies against homologous virus: Day	Antibodies against homologous virus: Titre	W.B.C.	Differential count
C	S.B.**	23 mos.	Aug. 6	1	ECHO 9	—	—	Aug. 4— 5000	Polys. 1050 Lymphs. 3800
						—	—		
D and V	J.L.V.*	12 mos.	Aug. 8	6	—	6	0 C. F. Adeno	Aug. 13—10,600	Polys. 2000 Lymphs. 8600
						47	1/32		
D and V	P.Gl.	2½ yrs.	Aug. 11	5	—	5	1/128 C. F. Adeno		Not done
						19	1/128		
D and V	L.O.**	2 mos.	Aug. 17	4	ECHO 22	4	0	Aug. 20—12,900	Polys. 3500 Lymphs. 9000
						41	1/32		
C	G.M.**	3 yrs.	? Aug. ?		Coxsackie B_5	—	—		Not done
						—	—		
D and V	G.B.*	13 mos.	Aug. 19	7	—	7	0 C. F. Adeno	Aug. 23—6600	Polys. 2376 Lymphs. 4224
						28	1/128		
D and V	D.T.**	12 mos.	Aug. 23	5	ECHO 10	5	0	Aug. 27—11,000	Polys. 4100 Lymphs. 6800
						—	—		
D and V	L.P.*	2 yrs.	Sept. 10	7	Adeno III	7	0 C. F. Adeno	Sept. 15—8300	Polys. 4980 Lymphs. 3071
						14	1/256		
D and V	V.N.**	2½ yrs.	Sept. 16	7	Polio I	7	I 0	Sept. 22—6900	Polys. 2415 Lymphs. 4200
						—	II 0		
							III 0		
						—	—		
D and V	B.C.**	18 mos.	Oct. 7	4	Coxsackie B_5	4	1/16	Oct. 10—6700	Polys. 2211 Lymphs. 4355
						15	1/64		
D and V	P.McC.*	5 yrs.	Oct. 16	6	Adeno III	6	0 C. F. Adeno	Oct. 18—7700	Polys. 5544 Lymphs. 2079
						20	1/128	Oct. 21—4300	Polys. 1806 Lymphs. 2408
D and V	P.Gr.	6 yrs.	Oct. 20	8	—	8	1/128 C. F. Adeno	Oct. 27—13.300	Polys. 8500 Lymphs. 4400
						17	1/128		
D and V	P.B.**	2½ yrs.	Oct. 30	5	Polio III	5	I 0	Nov. 3—9300	Polys. 6696 Lymphs. 2418
							II 0		
							III 1/12		
						9	I 0		
							II 0		
							III 1/32		
D and V	S.P.	17 mos.	Nov. 10	5	—	5	1/32 C. F. Adeno	Nov. 14—6300	Polys. 1890 Lymphs. 4284
						8	1/64		
C	D.L.	22 mos.	Nov. 21	9	Adeno I	—	—	Nov. 23—11,800	Polys. 9300 Lymphs. 2500
						—	—		
D and V	R.K.*	18 mos.	Nov. 28	7	—	7	1/8 C. F. Adeno	Dec. 4—5200	Polys. 1508 Lymphs. 3380
						18	1/64		
C	F.M.	7½ mos.	? Nov. ?		Adeno VII	—	—	Dec. 10—9100	Polys. 1638 Lymphs. 7371
						—	—		
D and V	R.C.*	1 mo.	Dec. 17	6	—	6	0 C. F. Adeno	Dec. 10—11,700	Polys. 4400 Lymphs. 6700
						22	1/32	Dec. 27—11,400	Polys. 5300 Lymphs. 5800
C	C.G.	12 mos.	Feb. 8	4	Adeno I	—	—	Feb. 9—10,400	Polys. 6200 Lymphs. 4000
						—	—	Feb. 19—7100	Polys. 3000 Lymphs. 3300
D and V	D.C.	8 mos.	Feb. 12	6	Adeno I	—	—	Feb. 17—5900	Polys. 1121 Lymphs. 4661
						—	—		
D and V	D.R.**	20 mos.	Feb. 21	3	Adeno I	3	0 N.T. / 0 C. F. Adeno	Feb. 23—9300	Polys. 7068 Lymphs. 1953
							Died within 2 days	Feb. 24—4700	Polys. 2538 Lymphs. 1974
D and V	L.S.	4 mos.	March 7	10	Adeno V	10	0 C. F. Adeno	March 10—10,100	Polys. 2400 Lymphs. 7500
						—	—		
D and V	S.M.*	10 yrs.	March 18	4	—	—2	0 C. F. Adeno	March 21—5000	Not done
						6	1/128		
D and V	L.G.**	2 mos.	March 20	7	Adeno VII	11	0 C. F. Adeno	March 19—20,000	Polys. 14,000 Lymphs. 3000
						39	0		
D and V	B.T.	3 mos.	March 21	6	Adeno V	6	0 C. F. Adeno	March 20—7700	Polys. 3542 Lymphs. 3850
D and V	B.H.	4 mos.	March 29	2	Adeno V	—	—	March 27—15,800	Polys. 4600 Lymphs. 9400
						—	—		

C—Control cases.
D & V—Diarrhœa and vomiting.
C. F. Adeno—Complement-fixation test.
N.T.—Neutralization test.
*—Details of clinical findings in Table III.
**—Details of clinical findings in text.

Another patient, D.R., whose rectal swab yielded an adenovirus type I, deserves special comment, mainly because the post-mortem findings are available. This patient died after four days of illness, of which two were spent in hospital. She was markedly dehydrated on admission with a fever of 102°F.; physical examination was otherwise negative. She was rehydrated by intravenous therapy; diarrhœa persisted until her demise. Her only sibling, aged eight months, developed explosive diarrhœa a few days later and was admitted promptly: his hospital course was uneventful; no viruses or bacterial pathogens could be isolated from his rectal swab. Unfortunately no blood samples could be obtained from this child for a complement-fixation test.

At post-mortem examination, aseptic arterial and venous thrombi and arterial emboli were found in the brain and lungs. Aseptic thrombi were also present under the mitral and tricuspid valve leaflets, presumably the site of origin of the emboli. The intestinal wall showed no ulcerations or other gross alterations. Microscopically there was hypertrophy of the Peyer's plaques with lymphoid hyperplasia. Samples of brain, heart and spleen were processed and inoculated into tissue cultures, but no viruses could be isolated.

Despite the absence of antibodies in the first serum, there is no conclusive evidence that the diarrhœa was the consequence of an adenovirus infection. It is, however, a reasonable assumption, since no neutralizing antibodies could be detected in the first serum; a rise in titre for adenoviruses in the sibling would have constituted an adequate proof.

In view of the somewhat unexpectedly high percentage of adenovirus isolations, we were interested in appraising the frequency of diarrhœa as a symptom in these infections over a larger series. With this in mind we collected from other sources in our laboratory 15 cases of adenovirus infection proven by complement-fixation test either alone or in combination with the isolation of an adenovirus. To these we added seven cases from this series, using the same criterion. As far as one can judge from the hospital record of these patients and checking back with the parents, taking into account the possible effect of antibiotics among

TABLE III.—CASES OF ADENOVIRUS INFECTION

	Sept. 10															
	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Days of illness
								Adm.	1st ser.							2nd ser.	
L.P.—2 years																	
Diarrhœa			———	———	———	———	———	———									
Vomiting			———	———													
Fever			———	———	———	———	———	———	———	———	———	———					
Conjunctivitis					———	———	———										
Rhinorrhœa					———	———	———	———	———	———	———	———	———				
Antibodies									0							1/256	
Virus isolation								Adeno 3									

	Aug. 19															
	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	28
							Adm.		1st ser.								2nd ser.
G.B.—13 mos.																	
Diarrhœa			———	———	———	———	———	———									
Vomiting			———														
Fever							———					———	———	———	———	———	
Antibodies									0								1/128
Virus isolation																	

	Aug. 8															
	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	47
								Adm.									2nd ser.
								1st ser.									
J.L.V.—12 mos.																	
Diarrhœa			———	———	———	———	———	———	———	———	———						
Vomiting			———	———													
Fever								———	———	———	———	———	———				
Pharyng. cong.								———	———	———	———	———	———				
Antibodies								0									1/32
Virus isolation																	

	March 18															
	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	.....
	1st ser.			Adm.				2nd ser.								Disch.	
S.M.—10 years																	
Diarrhœa			———	———	———	———	———	———									
Fever			———	———	———	———	———	———									
Cough			———	———	———	———	———	———	———	———	———	———	———	———			
Rhinorrhœa			———	———	———	———	———	———	———	———	———	———	———	———			
Antibodies	0							1/128									
Virus isolation																	

	Oct. 16															
	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	20
				Adm.				1st ser.				Disch.					2nd ser.
P.McC.—5 years																	
Diarrhœa				———	———	———	———										
Vomiting			———	———													
Abd. pain			———	———													
Fever			———	———	———	———	———										
Pharyngitis				———	———	———	———	———	—	—	—	—	—				
Conjunctivitis					———	———	———	———	—	—	—	—	—	—	—		
Antibodies								0									1/128
Virus isolation								Adeno 3									

	Nov. 28															
	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	18
									Adm.				Disch.				2nd ser.
									1st ser.								
R.K.—18 mos.																	
Diarrhœa			———	———	———	———	———	———	———	—	—	—					
Low-grade fever							—	—	—	—	—	———	———				
Antibodies									1/8								1/64
Virus isolation																	

	Dec. 17																	
	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22
								1st ser.					Adm.				Disch.	2nd ser.
R.C.—1 mo.																		
Diarrhœa			———	———	———	———	———	———	———	———	———	———	—	—	—			
Vomiting			———	———	———	———	———	———	———	———	———	———	———	—	—	—	—	
Low-grade fever			———	———	———	———	———	———	———	———	———	———	———	———	———	———		
Cough													———	———	———	———		
Rhinorrhœa													———	———	———	———		
Antibodies									0									1/32
Virus isolation																		

other factors in producing this symptom, diarrhœa was a relatively conspicuous symptom in 11 out of 22 cases, an average of 50%. This had already been suspected by Tyrrell *et al.*,[7] who stated: "The normal patterns of clinical infection [with adenoviruses] in childhood have yet to be discovered.... Perhaps, in some cases, alimentary-tract symptoms dominate the picture. . . . In the epidemic we observed, we think the gastro-intestinal symptoms were due to the virus."

The complement-fixation test for influenza carried out in 27 cases of diarrhœa and vomiting was consistently negative. This test was performed mainly to see if there was any scientific basis for the common diagnosis of "intestinal flu" made in cases of this nature during the winter.

In view of some resemblance between influenza and the respiratory syndrome caused by the adenovirus infection, one is tempted to associate this virus, rather than the influenza virus, with a respiratory-enteric type of illness. Several findings can be put forward in favour of this hypothesis. In 1954, a report by Goodall[8] on "gastric flu" or "winter vomiting disease" in adults also gave uniformly negative results for influenza by complement-fixation test. In the present series, adenoviruses exclusively were isolated in the winter and spring periods. We were also impressed in this study by the occurrence of diarrhœa with or without respiratory symptoms in the father or mother or both parents in three of our patients with diarrhœa and vomiting from whom an adenovirus was isolated. One of these, P. McC., had a fourfold increase in antibodies. In none of our other positive cases did we record a similar finding on reviewing the family history. It is also of great interest in this regard that a definite respiratory-enteric type of illness occurred as the result of proven adenovirus infection in a boy aged 5 years, P. McC., and in another aged 10 years, S. M.—the two positive cases in this series over the 3-year age level.

The number of enteroviruses isolated is too small to permit any general conclusion. However, since a rising titre in antibodies was demonstrated by neutralization test in the majority of the cases of the diarrhœa group, a few clinical observations may be worthy of note.

V.N., from whom a polio virus type I was isolated, is a 2½-year-old child who had a seven-day episode of low-grade fever, diarrhœa and vomiting, plus vague abdominal pain. His course was benign and he did not require any intravenous therapy. His first serum showed no antibodies against any of the polio strains.

P.B. had a similar seven-day illness, which started like a simple cold with vomiting for three days and two semi-liquid stools; a low-grade fever was present in the first few days. The finding of a questionable stiff neck in this case failed to lead to the real etiology and was interpreted as meningismus due to gastro-enteritis; the lumbar puncture examination was negative. A poliovirus type III was isolated from the rectal swab, and a slight rising titre for polio III and none for the other types could be detected within five days.

B.C., in whom a Coxsackie B_5 virus was found, showed a biphasic type of illness: two episodes of fever, vomiting and diarrhœa that were five days apart. A rising titre was demonstrated by neutralization test.

The control patient, G.M., who had the other Coxsackie B_5 virus, had had a three-week episode of harsh cough and anorexia, with intermittent vomiting and fever that ended one week before her visit to the outpatient clinic, but she had had no diarrhœa.

D.T., aged 12 months, was admitted to hospital in August, with a clinical picture of cough, red throat and temperature up to 102° F. at the onset, followed shortly by vomiting and watery green stools. The one-week duration of illness was relatively mild although intravenous rehydration was necessary. An ECHO type 10 virus was isolated from her rectal swab, and her first serum, the only one available, showed no detectable antibodies to ECHO type 10.

L.O., two months old, had a five-day episode of uncomplicated afebrile diarrhœa and vomiting, with mild dehydration, for which she was admitted in August. She was given fluids intravenously for a very short period, and rehydration was then carried out orally. An ECHO type 22 virus was isolated from her rectal swab, and a definite rising titre was demonstrable in the convalescent serum.

The control patient (aged 23 months) with an ECHO 9 virus infection was admitted in August for investigation and control of petit mal seizures. After a few days in hospital, she developed an unexplained fever to 102° F. which slowly dropped within three days. She had no diarrhœa. One sibling at home, aged 9, had severe headache and unexplained fever for a few days at the same time.

In all the positive cases (Table II) the white blood cell count deserves attention. With practically no exceptions it was between 5000 and 10,000 with a definite predominance of lymphocytes of more than could be expected from the age of the child in most cases. In adenovirus infections a transient polynucleosis seemed to occur at times in the early phase, similar to the one described in poliomyelitis.

Table I discloses the type of virus recovered from rectal swabs in the two groups of children. Although the number of viruses isolated in the diarrhœa group is larger than in the control group, no specific type of virus can be found significantly associated with the syndrome of diarrhœa and vomiting. Adenoviruses type III and V were found exclusively in the diarrhœa group, but the number isolated is too small to be of statistical significance.

In the light of recent work and the present findings (especially from their correlation with the clinical picture) it appears that diarrhœa is a variable symptom that follows infection from several

different agents. The occurrence of diarrhœa and its importance seems dependent on several factors, including mainly the type of agent, the host, his age, and status of immunity. One gathers the impression that this syndrome of diarrhœa and vomiting will finally be added to the list of possible manifestations of an infection with any one of these viruses, just as, one after the other, aseptic meningitis, pleurodynia, myocarditis, encephalitis, and even paralytic disease or summer "grippe" have been proved to result from apparently the same Coxsackie B infection.

The low isolation rate of enteroviruses in this series as compared with previous series[2-3] is difficult to explain. Technical difficulties are probably the most important factors. However, the prevalence of adenoviruses in this region as a cause of infection manifested by diarrhœa and vomiting alone, or other combination of symptoms,[9-10] may account for this low isolation rate of enteroviruses. Adenoviruses, on the other hand, are less likely to be present in rectal swabs than in other more suitable specimens for isolation, such as throat washings. This may possibly explain why in spite of the prevalence of these viruses the overall isolation rate in this series is still quite low. In fact, five cases of adenovirus infection with simple diarrhœa and vomiting in this series were picked up by the complement-fixation tests only, despite more careful attempts at isolating the virus from the rectal swab. It is probable that many more would have shown a rising titre for adenoviruses had sera been available in all cases.

SUMMARY

Over a period of 10 months from July 1958 to May 1959, 14 viruses were isolated from rectal swabs of a group of 74 infants and children with acute self-limited episodes of diarrhœa and vomiting, as compared with five viruses in a control group of 62 children. At least five additional cases of viral infection were discovered by the complement-fixation test in the diarrhœa group.

In over half of the positive cases in the test group, as well as in the control group, the agents were adenoviruses; in the winter and spring periods only adenoviruses were isolated.

These findings point to a prevalence of adenovirus infections probably greater in this region during 1958-59 than reported elsewhere. The use of HeLa tissue cultures as well as monkey kidney also partly explains this difference, even though there was often evidence of the presence of adenovirus in both media.

It appears that diarrhœa from viral infection in children is only a symptom of variable frequency dependent on several factors—the type of agent, the host, his age, status of immunity, etc. Most viruses isolated so far from rectal swabs seem able to produce diarrhœa and vomiting as part of their infectious process. Their ability to do so varies apparently from one agent to the other. It is estimated from our data that the average incidence of diarrhœa with adenovirus infection is in the range of 50%. However, significant variations from this may probably be found in selective age groups, as well as under the influence of other factors.

The overall low isolation rate in this series leads us, in spite of a few reasonable explanations that are discussed, to seek an additional explanation in the possible existence of non-bacterial agents similar to those described in adults[4-6] and as yet not viable in tissue cultures.

REFERENCES

1. EICHENWALD, H. F. *et al.*: *J. A. M. A.*, **166**: 1563, 1958.
2. RAMOS-ALVAREZ, M. AND SABIN, A. B.: *Ibid.*, **167**: 147, 1958.
3. SOMMERVILLE, R. G.: *Lancet*, **2**: 1347, 1958.
4. GORDON, I., PATTERSON, P. R. AND WHITNEY, E.: *J. Clin. Invest.*, **35**: 200, 1956.
5. JORDAN, W. S., JR., GORDON, I. AND DORRANCE, W. R.: *J. Exper. Med.*, **98**: 461, 1953.
6. GORDON, I., INGRAHAM, H. S. AND KORNS, R. F.: *Ibid.*, **86**: 409, 1947.
7. TYRRELL, D. A. J., BALDUCCI, D. AND ZAIMAN, T. E.: *Lancet*, **2**: 1326, 1956.
8. GOODALL, J. F.: *Brit. M. J.*, **1**: 197, 1954.
9. CHANY, C. *et al.*: *Am. J. Hyg.*, **67**: 367, 1958.
10. JORDAN, W. S., JR. *et al.*: *Ibid.*, **64**: 336, 1956.
11. HODGES, R. G. *et al.*: *Ibid.*, **64**: 349, 1956.
12. KJELLEN, L., ZETTERBERG, B. AND SVEDMYR, A.: *Acta pædiat.*, **46**: 561, 1957.

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RÉSUMÉ

Les présentes recherches furent entreprises dans l'intention de découvrir un agent viral en relation avec les épisodes sporadiques ou épidémiques de diarrhée et vomissements observés au cours d'une année dans un hôpital pour enfants et de déterminer dans la mesure du possible le tableau clinique correspondant à chaque type de virus.

De juillet 1958 à mai 1959, des échantillons de selles (écouvillons) furent prélevés chez 74 enfants souffrant de diarrhée ainsi que chez 62 enfants témoins du même âge, à l'hôpital Montreal Children's; ces échantillons furent choisis de façon à éliminer les diarrhées d'origine bactérienne ainsi que les diarrhées d'apparence non infectieuse. Dans les cas de diarrhée, des échantillons de sang furent aussi prélevés à la phase aiguë et à la phase de convalescence. Les échantillons furent traités, à de légères modifications près, selon la méthode de Alvarez et Sabin (telle que décrite dans le *J. A. M. A.*, 167: 147, 1958) et ensemencés sur cultures de tissus HéLa et reins de singe.

Tout agent cytopathogénique fut typé contre les sérums connus: Polio, Coxackie A9 et B 1 à 5, ECHO 1 à 19 inclusivement, sauf le 4, plus ECHO 22, et Adeno 1 à 7 inclusivement. Les épreuves de fixation du complément pour influenza et adénovirus furent aussi faites sur les deux sérums, dans 28 cas de diarrhée. Les résultats obtenus sont résumés dans les Tableaux I, II et III.

Il convient de souligner en tout premier lieu ici, l'importance des adénovirus; ils constituèrent plus de la moitié des isolements dans les deux groupes d'enfants (diarrhée et témoins). Grâce au test de fixation du complément, cinq cas additionnels d'infection à adénovirus furent découverts. Ce fut le seul virus isolé tout au cours de l'année avec une fréquence à peu près constante et le seul à être retrouvé chez les enfants de plus de trois ans, ainsi que le seul virus isolé durant la période hiver-printemps.

Plusieurs constatations mentionnées dans cet article invitent à rejeter sur ce virus, plutôt que sur celui de l'influenza, la responsabilité de ce que plusieurs appellent sans fondement scientifique la "grippe intestinale". La plupart des virus isolés des selles jusqu'à présent, semblent capables de déclencher des épisodes de diarrhée et vomissements, de sorte qu'il faut apparemment considérer ces manifestations comme des symptômes dont la fréquence varie sous l'influence de plusieurs facteurs, l'agent en cause, l'hôte, son âge, son état d'immunité, etc. A titre d'exemple tiré de nos résultats au laboratoire de diagnostic des virus, la fréquence de ces symptômes en association à une infection à adénovirus est de 50% au moins.

Le nombre restreint de virus isolés au cours de la présente étude est décevant; en dépit de plusieurs explications valables, telles que la prévalence ici d'adénovirus, la difficulté relative d'isolement de ces virus à partir des selles et autres difficultés techniques, on est tenté d'offrir en guise d'explication supplémentaire, l'existence d'autres agents, (démontrée chez l'adulte) mais qui ne seraient pas viables en culture de tissus. J.J.