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Stool viruses in babies in Glasgow

3. Community studies

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SUMMARY

Twenty-seven babies from one deprived housing area in Glasgow were followed-up regularly, for periods varying between 2 months and 11 months (mean 7 months), in a prospective study of the viruses to be found in their stools by electron microscopy. Weekly stool specimens were collected in the home together with a history of the baby's health. Additional stool specimens were obtained, up to a maximum of one per day, during admissions to hospital. Over 500 specimens were obtained at home and another 320 in hospital. A wide variety of viruses (over 200 recognizates) were detected and it has been possible to plot their temporal relation to disease episodes. It became apparent that virus excretion was frequently unaccompanied by evidence of illness and it has not been possible to describe a typical illness syndrome associated with any of the morphological types of virus observed.

The results suggest that, in one area of Glasgow at least, patterns of virus excretion in young babies are complex and will need further elucidation before the need for a vaccine to prevent infantile diarrhoea could be defined.

INTRODUCTION

Examination of stools by electron microscopy (EM) for virus particles is rapidly becoming a standard part of paediatric practice. Yet, since virus detection does not alter management of infants and children with diarrhoea, their presence may

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be too readily regarded as identifying the causative agent. Reports of virus excretion by apparently normal babies (Totterdell, Chrystie & Banatvala, 1976; Murphy, Albrey & Crewe, 1977; Madeley, Cosgrove & Bell, 1978) and of multiple viral infections in babies with diarrhoea (Madeley *et al.* 1977) have meant that a pathogenic role for these viruses has become more difficult to define. Illness requiring hospital admission is contracted at home but most studies of the viruses found in diarrhoea have been made in hospital populations. A prospective EM study of babies in the community has not been reported hitherto.

An opportunity to do such a prospective study of the faecal viruses to be found during regular surveillance came during an investigation into the growth and development in a deprived inner city area, where we noted a high incidence of diarrhoea. Regular examination of faeces from 27 infants by electron microscopy over several months allowed observation of virus excretion before, during and after a variety of trivial and more serious illnesses at home and in hospital.

A stool was obtained from each baby at a regular home visit and more frequently while in hospital. As a result we obtained a large number of stools, and a considerable amount of data from examining them. It would have been very cumbersome to analyse these data under one heading and we have therefore divided them into two parts, investigations in the home and investigations in hospital. We recognize that this is arbitrary and not a true distinction but have done it in the interest of clarity.

MATERIALS AND METHODS

Study area

This was provided by a deprived urban community with high unemployment and family incomes frequently supplemented by Social Security benefits. All the babies came from a municipal housing estate of some half-dozen streets of ill-kept tenement buildings. The houses consisted of 2–5 room apartments with inside toilets, running hot and cold water and cooking facilities. Frequently, though, these services had been vandalized and were unusable, but some homes were well furnished and maintained.

Frequently three generations of a family inhabited a single home, sometimes with considerable overcrowding, and other branches of the family often lived in the same area. It was therefore possible for the care of individual babies to be shared among several adults and in more than one home depending on circumstances. This resulted in the baby's surname being changed on occasion and made the follow-up of some of the babies difficult. We are very much indebted to the local Health Visitors, whose knowledge of local social mores and family ramifications was invaluable.

In these circumstances the baby's effective family was hard to define and we have omitted data, and analysis, of siblings, family sizes and other social indices as being meaningless, if not actively misleading. In addition many of the families owned a dog which was rarely under control or restrained, and the extent to which these dogs could be disease vectors was unknown and uninvestigated.

Patients

Twenty-seven babies living in this area were selected at different times between February 1976 and February 1977. Six babies were observed from birth, 9 were selected from the Health Visitors' list of babies recently discharged from maternity units, and the remaining 12 were recruited after an admission to hospital during their first year of life. The average age on admission to the study was 2·7 months.

Home visits

Each household was visited weekly when a history of the baby's health during the period since the previous visit was obtained from the mother, and a sample of the baby's faeces was collected. Mothers were asked to scrape the faeces from the nappy, using a wooden spatula, into a clean container preferably within the 24-h immediately before the next visit. Babies were observed briefly at each visit and a physical examination was carried out when any illness was reported, or signs noted.

Duration of follow-up

The follow-up periods for individual babies varied from 2 to 11 months (mean 7 months). It was our intention to follow each baby till his or her first birthday, but this was not always possible. Incomplete follow-up was due to leaving the housing area (4 babies) or domestic problems (8 babies). Three children were recruited at 7, 11 and 14 months old, and they were followed-up beyond 1 year of age. The remainder were followed as planned to 1 year old, or until the study was terminated in April 1977.

Hospital admissions

Study of the babies continued during hospital admissions and we also studied babies from the same housing area admitted to hospital but who could not, for various reasons, be followed-up at home. The hospital data in this report includes only those admissions where three or more stools were obtained. Another 14 admissions have not been included because an insufficient number of stool specimens were examined.

Clinical categories

(1) *Assessment of illness in the home.* Illnesses described by the mother were assessed by one of us (T.M.S) at the time of the visit and before the results of laboratory investigations were available. They were allocated to four categories:

(*a*) 'Diarrhoea' was defined as a change in bowel habit with either an increase over the usual frequency of stools, or at least one watery stool.

(*b*) 'Respiratory' included signs of respiratory tract involvement, other than trivial nasal catarrh, which were reported by the mother or observed at the weekly visit. In some cases there was clinical evidence of lower respiratory involvement at the weekly examination, but a separate category has not been used.

(*c*) 'Diarrhoea and respiratory' included those babies with diarrhoea as defined above with an accompanying respiratory component.

(*d*) 'Rash'. These were all erythematous and maculo-papular and several were probably measles, though no virological confirmation was attempted.

(2) *Hospital admissions.* With the greater precision in diagnosis possible in hospital, the categories were more accurately defined. Six categories have been used: (*a*) Diarrhoea, (*b*) Diarrhoea and upper respiratory tract illness (URTI), (*c*) Diarrhoea and lower respiratory tract illness (LRTI), (*d*) URTI alone, (*e*) LRTI alone, and (*f*) Other. The last category includes conjunctivitis (1 baby), nappy rash (2 babies), social problem (2 babies), fractured hip (1 baby), dwarfism (1 baby) and no detected abnormality (1 baby).

Laboratory investigations

Stool samples were prepared for electron microscopy as previously described (Madeley *et al.* 1977). Stool extracts were initially inoculated onto cell cultures but after the beginning of March 1976 this was discontinued as no new virus patterns had been detected. Stools from babies in hospital were routinely cultured bacteriologically by standard methods but this was not done on stools from babies in the home.

RESULTS

Investigations in the home

Figure 1 indicates the stool specimens obtained from each baby and also the duration of surveillance. Each horizontal line indicates the period of active follow-up; a vertical stroke indicates a stool specimen and a letter over it indicates a virus identified electron microscopically. The black and white boxes represent the time and duration of hospital admissions of which there were 26. Details of these hospital admissions are given below.

The maximum number of stools that could have been obtained from home visits in this study was 677 (number of babies × number of weeks followed-up, excluding time spent in hospital). Five hundred and twenty-eight (78%) were actually obtained. The deficiency of 149 was due to various causes, of which the most common were the mother's failure to obtain the specimen, temporary absence of the family from home due to domestic upheaval, and staff holidays. In addition, a further 20 stools were obtained from babies 18–21, 24 and 26 while they were still in the postnatal ward.

The viruses detected in the stools of each baby are indicated in Fig. 1 and summarized in Table 1. Seventy-four home stools were found to contain virus and four of them contained more than one morphological type. Positive stools were obtained from 22 babies and no viruses were found in the stools of the other 5, though one (No. 26) was found to excrete viruses while in hospital. Adenovirus was the most common virus to be detected and repeated excretion was not unusual. Few of these adenoviruses grew in cell cultures and it was not possible to type them by the usual methods. Further investigations are in progress and will be the subject of a separate report.

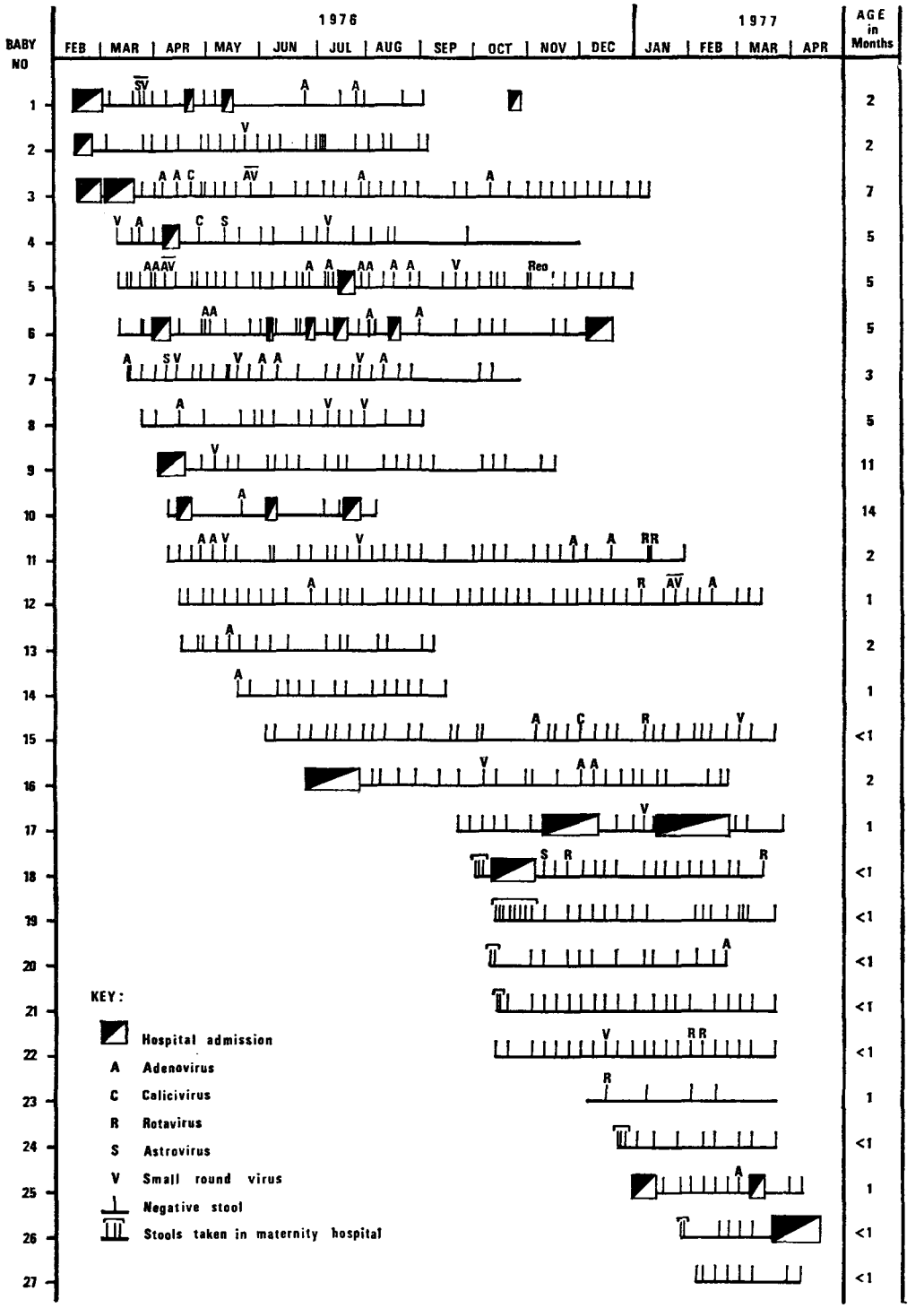

Fig. 1.

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Table 1. *Duration of follow-up and results from stool specimens taken at home*

						Illnesses					Home viruses			
Baby no.	Duration of home follow-up (weeks)	No. of weeks in hospital	Total duration of follow-up (weeks)	No. of admissions to hospital	No. of stools obtained in the home	Resp. tract	Diarrhoea	Resp. and diarrhoea	Other	Total	Rotavirus	Astrovirus	Calicivirus	Adenovirus
1	29	3	32	4	14	2	3	1	—	6	—	1(1)‡	—	2
2	27	1·5	28·5	1	24	3	1	—	—	4	—	—	—	—
3	43	4·5	47·5	2	38	5	—	1	1	7	—	—	1	5 (1)
4	35	1·5	36·5	1	17	—	5	—	—	5	—	1	1	1
5	41	1·5	42·5	1	46	3	4	2	—	9	—	—	—	9 (1)
6	33	7	40	6	24	1	1	—	—	2	—	—	—	4
7	33	—	33	—	26	3	1	—	1	5	—	1	—	4
8	25	—	25	—	17	2	3	—	—	5	—	—	—	1
9	30	2·5	32·5	1	21	1	—	—	1	2	—	—	—	—
10	15	3·5	18·5	3	5	1	1	—	—	2	—	—	—	1
11	43	—	43	—	34	3	3	1	—	7	2	—	—	4
12	48	—	48	—	43	2	2	1	—	5	1	—	—	3 (1)
13	23	—	23	—	16	1	—	—	—	1	—	—	—	1
14	17	—	17	—	14	—	1	—	—	1	—	—	—	1
15	42	—	42	—	35	5	—	—	1	6	1	—	1	1
16	31	5	36	1	22	4	—	—	—	4	—	—	—	2
17	16	12	28	2	13	1	2	—	—	3	—	—	—	—
18	22	3	25	1	17	1	—	—	1	2	2	1	—	—
19	20	—	20	—	16	1	—	1	1	3	—	—	—	—
20	19	—	19	—	12	1	—	—	—	1	—	—	—	1
21	23	—	23	—	19	1	1	—	—	2	—	—	—	—
22	24	—	24	—	22	2	—	1	—	3	2	—	—	—
23	15	—	15	—	4	1	—	—	—	1	1	—	—	—
24	12	—	12	—	8	—	1	—	—	1	—	—	—	—
25	10	3·5	13·5	2	9	—	1	—	—	1	—	—	—	1
26	7	3·5	10·5	1	4	1	—	—	—	1	—	—	—	—
27	9	—	9	—	8	1	—	—	—	1	—	—	—	—
Total	692	52	744	26	528	46	30	8	6	90	9	4 (1)	3	41 (2)
Av.	26	—	27	—	20	51 %	33 %	9 %	7 %	100 %	12 %	5 %	4 %	53 %

The small round viruses (SRVs) were a heterogeneous group of virus-like objects between 25 and 35 nm in diameter that convincingly resembled viruses in appearance. They could easily be distinguished from debris of similar size by the 'collar' of negative stain that surrounded them. Within one stool and, occasionally, in several stools from one baby, they were consistent in size and appearance but different recognizates (Madeley & Kay, 1978) varied. It is possible that some were cubic bacteriophages but there is no way to demonstrate this. The astroviruses and caliciviruses could be distinguished from other SRVs by possessing characteristic morphologies (Plate 1). A detailed comparison of these two viruses has been published elsewhere (Madeley, 1979). The relation of individual viruses to disease is recorded and discussed below.

The type and duration of home illnesses recorded during the survey and their association with virus excretion are shown in Fig. 2. The width of each box is

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Table 1 (*cont.*)

Baby no.	Home viruses: Reovirus	Home viruses: SRV*	Home viruses: Total	Association virus/illness: Rotavirus	Astrovirus	Calicivirus	Adenovirus	SRV*	Total	Proportion†	Association of viruses with types of illness: Respiratory tract	Diarrhoea	Respiratory and Diarrhoea	Other
1	—	1 (1)	4	—	1 (1)	—	2	1 (1)	4	4/4	1A§	1A	1S 1V	—
2	—	1	1	—	—	—	—	—	—	0/1	—	—	—	—
3	—	1 (1)	7	—	—	1	3	—	4	4/7	—	—	2A 1C	1A
4	—	2	5	—	—	—	1	1	2	2/5	—	1A 1V	—	—
5	1	2 (1)	12	—	—	—	5	—	5	5/12	1A	3A	1A	—
6	—	—	4	—	—	—	—	—	—	0/4	—	—	—	—
7	—	3	8	—	1	—	1	—	2	2/8	1S	—	—	1A
8	—	2	3	—	—	—	—	1	1	1/3	1V	—	—	—
9	—	1	1	—	—	—	—	—	—	0/1	—	—	—	—
10	—	—	1	—	—	—	1	—	1	1/1	—	1A	—	—
11	—	2	8	2	—	—	2	2	6	6/8	1A	2R 1A 2V	—	—
12	—	1 (1)	5	1	—	—	1	—	1	1/5	—	—	1R	—
13	—	—	1	—	—	—	—	—	—	0/1	—	—	—	—
14	—	—	1	—	—	—	—	—	—	0/1	—	—	—	—
15	—	1	4	1	—	1	1	—	3	3/4	1R 1A 1C	—	—	—
16	—	1	3	—	—	—	1	—	1	1/3	1A	—	—	—
17	—	1	1	—	—	—	—	—	—	0/1	—	—	—	—
18	—	—	3	—	—	—	—	—	—	0/3	—	—	—	—
19	—	—	—	—	—	—	—	—	—	0/0	—	—	—	—
20	—	—	1	—	—	—	—	—	—	0/1	—	—	—	—
21	—	—	—	—	—	—	—	—	—	0/0	—	—	—	—
22	—	1	3	—	—	—	—	—	—	0/3	—	—	—	—
23	—	—	1	1	—	—	—	—	1	1/1	1R	—	—	—
24	—	—	—	—	—	—	—	—	—	0/0	—	—	—	—
25	—	—	1	—	—	—	1	—	1	1/1	—	1A	—	—
26	—	—	—	—	—	—	—	—	—	0/0	—	—	—	—
27	—	—	—	—	—	—	—	—	—	0/0	—	—	—	—
	1	20 (4)	78	5	2 (1)	2	19	5 (1)	32	32/78	2R 1S 1C	2R 8A	1R 1S 1C	2A
	1 %	26 %	100 %	5/9‖ 56 %	2/4 50 %	2/3 67 %	19/41 46 %	5/20 25 %	32/78 41 %		5A1V (10)¶	3V (13)	3A 1V (7)	(2)

* Small round virus.
† Proportion: viruses associated with illness/total number of viruses found in the patient's stools.
‡ Number in parentheses = numbers of stools in which the virus was found in association with another virus.
§ A, adenovirus; C, calicivirus; R, rotavirus; S, astrovirus; V, small round virus.
‖ Proportion: viruses associated with illness/total number of occasions the virus was found.
¶ Total.

proportional to the duration of illness and, for the sake of clarity, only stools positive for virus are included in this figure. There were 90 recorded episodes of illness, of which 30 were diarrhoea, 46 were respiratory illnesses, 8 combined diarrhoea with respiratory signs and 6 were skin rashes. Babies 13, 14, 20 and 23–27 had only one home episode while numbers 1, 3, 5, 11 and 15 had at least six episodes each. Some babies (nos. 2, 3, 7 and 15) had repeated respiratory ailments while others (nos. 1, 4, 5 and 8) had repeated episodes of diarrhoea. Baby 11 had four episodes of respiratory illness as well as four episodes of diarrhoea. The admissions to hospital, though indicated in the Figure, are not included in the analysis here but details are given below.

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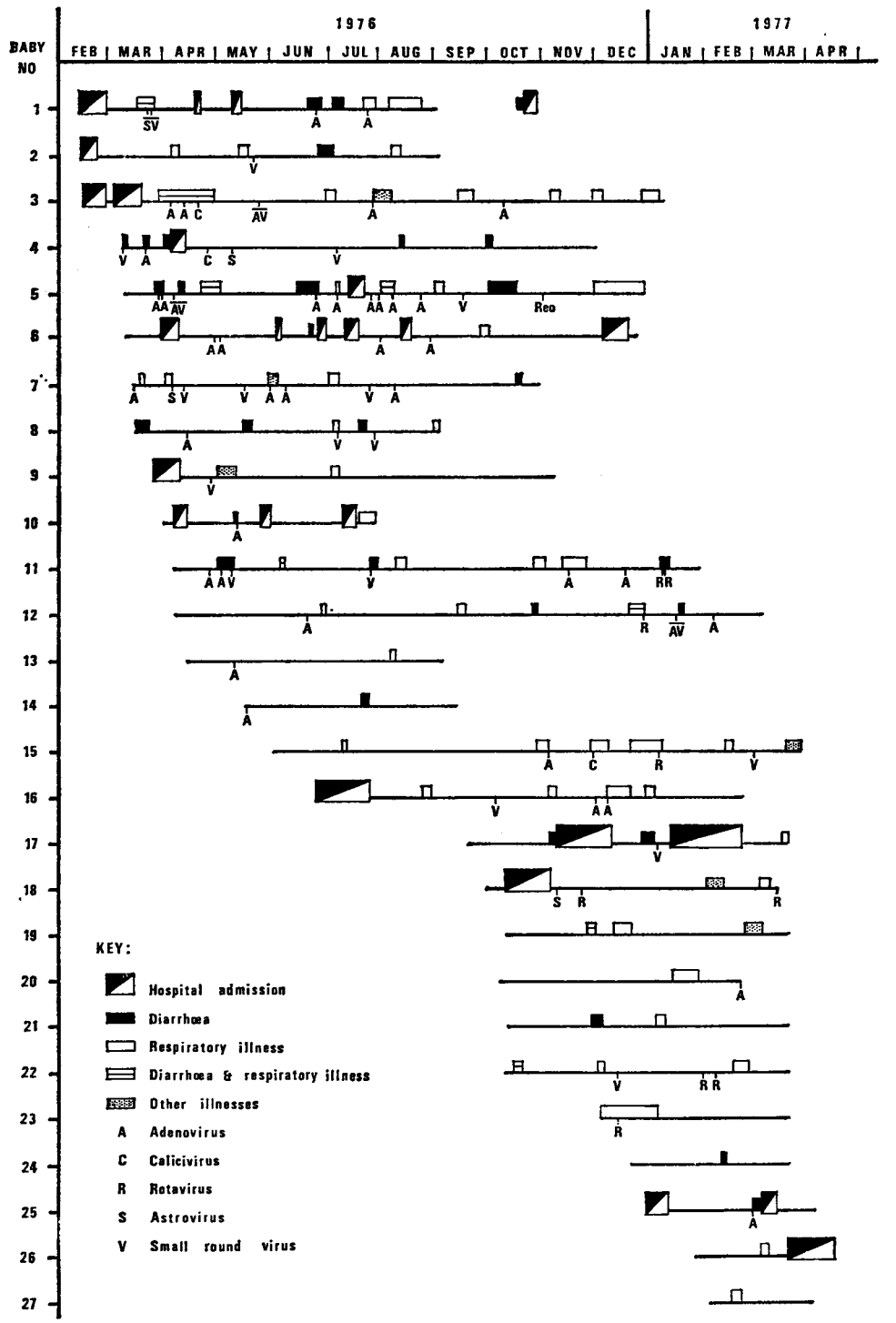

Fig. 2.

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The viruses found in the stools obtained at home are shown in Figs. 1 and 2 and these results are summarized in Table 1, where each virus-positive stool has been recorded as a separate entity although, where the same virus is found in consecutive stools taken a short time apart, it is likely that they were part of the same episode. Two such examples are the diarrhoeal episodes of baby 5 in March 1976 (2 adenoviruses) and baby 11 in January 1977 (2 rotaviruses).

In all, 78 stool specimens were found to contain virus but only 32 (41 %) were associated with a reported episode of illness. Thirteen of these were diarrhoea, 10 were respiratory, 7 were diarrhoea with a respiratory component and 2 were rashes. The remaining 42 virus-positive stools came from apparently healthy babies. All the morphological types of virus that we observed were found in the stools of both normal and ill babies. The numbers are too small to allow a more detailed analysis but no one virus stands out as having a clearly stronger association with disease than any other.

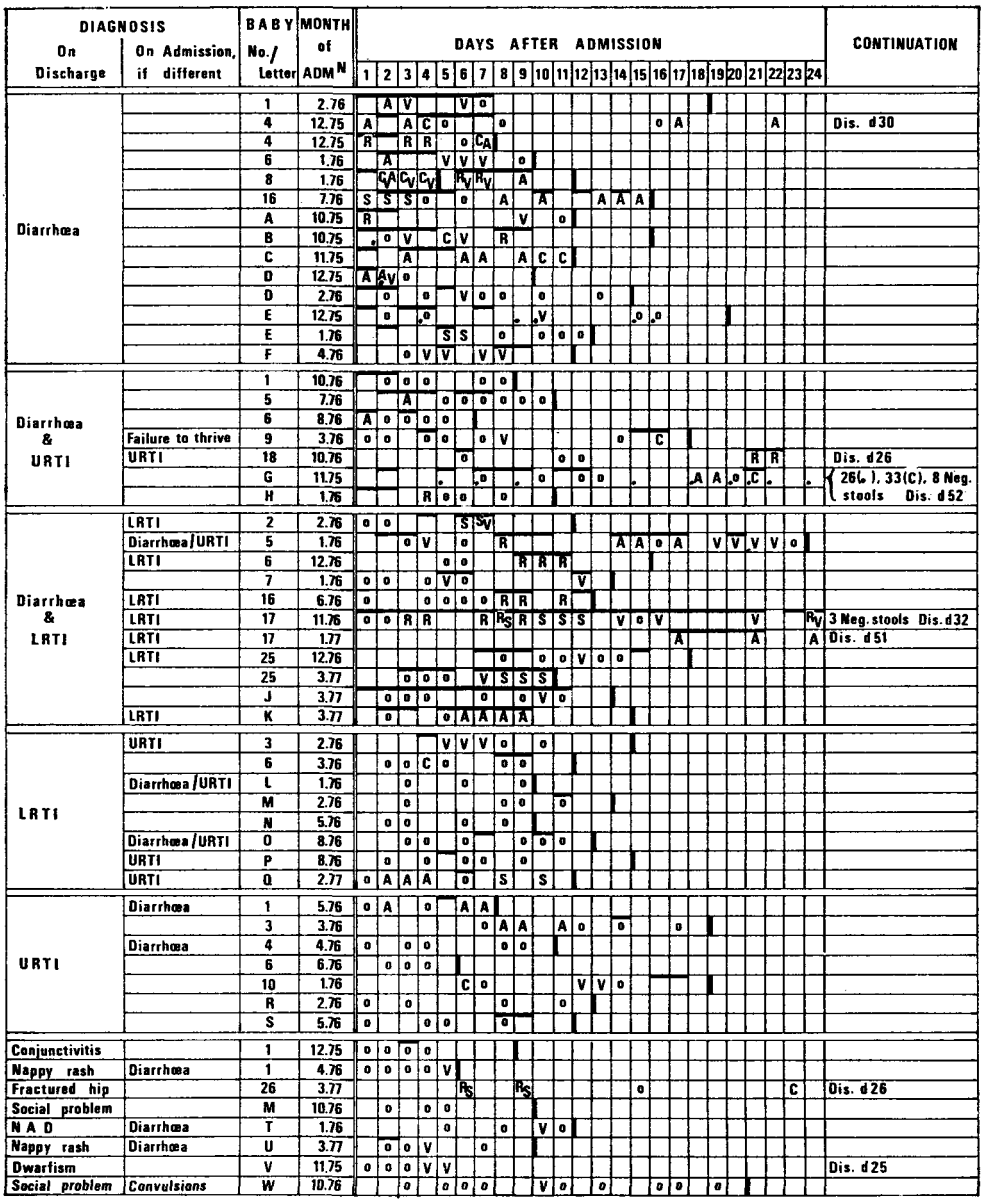
Investigations in hospital

During the study 13 babies were admitted to hospital on a total of 26 occasions. Seven babies had also been admitted on a total of eight occasions before the survey started and another 27 babies from the same housing area were also admitted shortly before it began or while it was in progress. Seven of these babies were admitted twice making a total of 68 admissions from these 54 babies alone over a period of 18 months. In 55 of these admissions three or more stools were examined with the results shown in Fig. 3. Each admission is shown day by day with the results of electron microscopy and any bacterial pathogens identified.

The horizontal bars in the daily squares represent an entry in the medical or nursing notes or in the fluid chart indicating loose, frequent or watery stools. Most babies who had a record of such 'abnormal' stools had several entries of this kind separated by days of apparently normal stools. One baby (no. 17 in November 1976) had these apparently abnormal stools for a full 3 weeks, though the diarrhoea was not severe enough to require the use of intravenous fluids.

Thirty babies were admitted with a history of diarrhoea and in 23 a continuing diarrhoea was noted after admission. In the remaining seven only the occasional loose or watery stool was noted, but such 'diarrhoea' was not considered important enough to be included in the discharge diagnosis. Conversely, eight babies sent into hospital with respiratory tract infection developed diarrhoea following their admission, though the patterns varied between intermittent loose stools and prolonged diarrhoea.

Of the 55 admissions, no viruses were found in the stools of 12 and, of the remaining 43, two or more viruses were seen in the stools of 20. Two and even three viruses were occasionally observed in a single stool specimen. Furthermore, individual babies showed frequent changes of viral flora, and this was particularly noticeable where diarrhoea was included in the final diagnosis on discharge. Fewer viruses were recorded from the babies who were not thought to have had a significant diarrhoea, but viruses of all the morphological types were found in their stools nevertheless.



In the third column numbered babies are those in the main follow-up series and lettered babies are those studied only in hospital.

Fig. 3.

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Table 2. *Adenovirus excretion*

No. of episodes/ baby	0	1	2	3	4	5	Total no. of episodes
No. of babies	27*	12	3	2	4	1	45

* Ten babies from the main follow-up series + 17 babies examined in hospital only.

Table 3. *Babies with multiple episodes of adenovirus excretion*

Baby no.	No. of episodes	No. of stools negative for adenoviruses between those positive (interval in weeks)
1	4	17 (8), 0 (6), 1 (4)
3	5	5 (2), 6 (6), 6 (8), 7 (10)
4	4	3 (2), 4 (1), 2 (12)
5	4	9 (8), 13 (11), 6 (1)
6	4	15 (12), 11 (12), 4 (2)
7	3	12 (11), 6 (8)
8	2	2 (12)
11	2	23 (32)
12	3	25 (30), 2 (3)
16	2	11 (20)
No. of babies 10	Total no. of episodes 33	

As with the stools obtained from home, no single virus was associated with a specific illness pattern; all the morphological types of virus were recognized in association with a variety of clinical situations – in diarrhoeal stools, in stools after the onset of diarrhoea, with or without other viruses first, or in apparently normal stools. No one virus is seen as inevitably associated with diarrhoea and, with the possible exception of adenoviruses (which were unlikely to be all the same serotype), no one virus predominated.

Relation between virus and disease

Before the relation between individual viruses and illness events can be discussed an attempt to define what constitutes a single episode of virus infection must be made, since the same morphological type of virus could be found on several occasions in the same baby. In this paper two episodes of virus excretion have been regarded as separate infections if there were at least two stools negative for that virus (though possibly positive for a different virus) or 6 or more days between positive stools. An interval of 6 days was chosen because it was usually the limit of the duration of excretion of rotaviruses in babies of this age (Davidson *et al.* 1975; Madeley *et al.* 1978). The detailed information is contained in Figs. 1–3 and Tables 1–3.

1. *Adenovirus.* Seventeen babies in the main follow-up series (babies 1–27) had adenoviruses in stools taken at home on at least one occasion and ten of these had multiple episodes. The total number of episodes of adenovirus excretion was 45 (Table 2), of which 28 were detected in the home and the remainder in hospital.

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Of those found in home stools 7 were associated with diarrhoea, 5 with other diseases, mostly respiratory, and the other 16 were in stools from apparently normal babies. Inspection of Fig. 3 suggests 18 episodes in hospital, a single episode in 15 babies and three in baby no. 4 during the two admissions in December 1975. Of the 42 adenovirus-positive stools in Fig. 3, only 18 were from loose or diarrhoeic stools. No consistent association with enteropathy can be deduced from these results but one might emerge when these adenoviruses are typed and this will be the subject of a further report. However, one apparently straightforward association (baby no. 6 in August 1976 whose first stool was both diarrhoeal and contained an adenovirus) is undermined by the observation that a stool taken a short while before in the home also contained an adenovirus. Between the two positive stools was an interval of 12 days in which one negative stool was obtained,

Table 3 lists the babies who had multiple episodes of adenovirus excretion and shows the intervals between positives by number of adenovirus-negative stools and weeks. Individual episodes were defined as indicated above but this is to some extent arbitarary; others analysing these data could prefer other criteria and find a different number of episodes. However, whichever definition is used multiple episodes of adenovirus excretion appear to be common.

2. *Rotavirus*. There were 19 episodes of rotavirus infection, of which 12 occurred in hospital and 7 in the home. These episodes involved 16 babies with one baby (no. 17) having two episodes in hospital and one baby (no. 18) having three episodes, one in hospital and two subsequently at home. Each rotavirus episode in these two babies was separated from another by at least two stools negative for rotavirus and a minimum of 15 days.

Only two of these home episodes were associated temporally with diarrhoea. The remaining five were found in normal babies (4) or in association with respiratory illness (1).

The 12 hospital episodes are more difficult to analyse. Inspection of Fig. 3 shows that 10 of these episodes coincided with loose or watery stools. No fewer than 8 of these, however, were found in stools obtained 6 or more days after admission, and may represent hospital-acquired infections.

3. *Astrovirus* (Plate IA). There were 11 episodes of astrovirus infection, 7 in hospital and 4 at home. Six were associated with diarrhoea (5 in hospital and 1 at home), three with respiratory infections and two involved normal babies at home and one an otherwise normal baby in hospital with a fractured hip. In six hospital episodes the virus was first seen on the fifth or subsequent day following admission and may also represent hospital-acquired infection.

4. *Calicivirus* (Plate IB). Before the start of this study caliciviruses had not been described in man. Morphologically indistinguishable viruses have been described in pigs, kittens and sea-lions (Andrewes, Pereira & Wildy, 1978). Consequently the virus found in a stool from baby G in October 1975 was a new discovery. Our preliminary report (Madeley & Cosgrove, 1976) has been confirmed by others (Flewett & Davies, 1976; McSwiggan, Cubitt & Moore, 1978). During the study a total of 14 episodes in 11 babies were recorded. Eight were associated with disease (4 with diarrhoea, 3 with respiratory illness and 1 with both respiratory and bowel

upset). The remaining six were not associated with disease. Baby 4 apparently had three episodes, of which only the first was associated with an illness.

5. *Other viruses.* One reovirus was observed and was identified as type 3. It was found in a stool from baby 5 taken at home and was not associated with illness. This observation prompted a reappraisal of those viruses identified as rotaviruses but no further reoviruses were discovered.

The remaining viruses were all 'small round viruses' (Plate Ic). Since they will not all have been identical, though generally similar in appearance, a detailed analysis is likely to be misleading. After the adenoviruses, which may themselves be of different serotypes, they form the second largest group of viruses found in stools from the home (Table 1). Inspection of Fig. 1 showed that possible reinfection is common (5 babies) and a large proportion (15 out of a total of 20 episodes 75%) are not associated with illness.

Bacteriology

Stools for bacteriological culture were taken routinely from those babies admitted to hospital with a diagnosis of diarrhoea. All were negative for pathogens except some of those from babies B, D, E, and G. Baby B had *E. coli* strain O119 in one stool while babies D, E and G had *E. coli* strain O125 in their stools during November and December 1975. These three babies were all in the same ward with some overlap between their admissions, consequently infection may have been transmitted from one baby to another.

DISCUSSION

This study records some of the viruses to be found during regular surveillance of a number of babies. In intention, it was similar to the Virus Watch Programs in New York and Seattle (Fox *et al.* 1966; Cooney, Hall & Fox, 1970) and surveillance in Junior Village (Bell *et al.* 1961). In scope it was much more circumscribed as it was confined mainly to a single technique. It was initiated after babies, under observation for a different purpose, had been noted to have frequent illnesses at home. The results confirm the high incidence of illness, particularly in some of the babies (nos. 1, 3, 4, 5, 6, 8, 11 and 15) who each had six or more episodes of illness including hospital admissions during follow-up. The illnesses included in the results are only those thought to be more than trivial and Fig. 2 gives a general impression of the health of these babies.

The results of this study do not make the causes of this morbidity any clearer. We looked only in stools for viruses and this is unlikely to provide much evidence about respiratory infections though respiratory viruses may pass through the gut unaltered. So far rotaviruses, astroviruses and caliciviruses have not been shown to cause respiratory illnesses; adenoviruses, reoviruses and some enteroviruses (typically SRVs in morphology) have been recovered from the nasopharynx but the adenoviruses we saw may not be the serotypes which cause upper respiratory tract infections, and the roles of reoviruses and enteroviruses in respiratory disease are also open to doubt. Nevertheless viruses were found in stools taken in

the home from babies with respiratory infection as often as from babies with diarrhoea (Table 1). Inspection of Fig. 2 does not reveal any consistent association between episodes of virus excretion and those of illness. A large number of stool specimens was obtained in the home (528) but a comparison of Fig. 1 with Fig. 3 suggests that only a small proportion of the total viruses present are likely to have been detected by weekly specimens. There was a high frequency of change in the type of virus excreted, especially during diarrhoea, and it is likely that many viruses were missed. The opportunity to acquire new viruses may be less at home than in hospital and consequently fewer viruses may have been missed than a straightforward comparison of Fig. 1 and 3 suggests. However, this may not be a valid assumption as the population of the housing area was very gregarious, with much close contact between families and consequent opportunity to acquire new viruses. For example, it was not always possible to know in which house the baby was to be found and the immediate blood relatives were by no means the babies' only contacts, with individual babies being moved from one home to another from time to time.

With only a small proportion of all the stools passed being examined, it is likely that any association found between virus and disease was lower than it should have been as stool specimens will not always have been collected early in a disease episode. However, more frequent visits to the home would have begun to distort the normal pattern by increasing the opportunities for introducing new virus or for spreading virus from one family to another, as well as producing unmanageable numbers of stools. Additionally, they would have required even more co-operation from the families with more invasion of their privacy. The co-operation received was excellent and to have asked for more would, we considered, have been unjustified and we decided to accept obvious limitations of our approach.

Nevertheless many viruses were detected in home stools. They included adenoviruses, rotaviruses, astroviruses, caliciviruses, a variety of small round viruses and a reovirus. They were often found in the stools of apparently healthy babies. Considerable morbidity was found and it is possible that minor illnesses associated with these viruses may have gone unrecorded, but these must have been trivial and certainly did not lead to hospital admission. This contrasts, for example, with the severe and even fatal role found for rotaviruses in Canada (Carlson *et al.* 1978).

With multiple stools being obtained from each baby, second or more episodes of virus excretion were detected in several babies. Since few viruses found in stools grow in cell cultures (Madeley *et al.* 1977) electron microscopy is the only method currently available which is capable of detecting every kind of virus. However, it is an insensitive method and substantial amounts of virus (up to the threshold level of detection which is about 10^6 particles/g of faeces) may remain undetected. Consequently it is difficult to define when an episode of virus infection ends. Reappearance of virus may represent reinfection, recrudescence of a primary infection or a continuing infection where the amount of virus being excreted is variable, periodically rising above the threshold of detection.

Previous studies (Davidson *et al.* 1975; Flewett & Woode, 1978; Madeley *et al.* 1978) suggested that rotavirus excretion usually declines over a few days and

remains undetectable thereafter, though follow-up in these studies was short. It seems more likely, therefore, that recurrent excretion of virus after an interval of days, or weeks, with several stools devoid of that particular virus (though other viruses may be found) represents either reinfection with the same or a different serotype or a dormant infection being reactivated. Recent results (A. H. Kidd, personal communication) show that individual babies may excrete one adenovirus serotype for up to several months with unpredictable change to a different serotype from time to time. It seems reasonable to assume that the three episodes of rotavirus excretion by baby 18 in hospital in October 1976 and at home in November 1976 and in March 1977 are separate, particularly the last two with more than 3 months and 13 negative stools between them. Fonteyne, Zissis & Lambert (1978), and Rodriguez *et al.* (1978) have reported second infections by different serotypes of rotavirus. There seem now to be at least four human serotypes and our findings could be explained as sequential infection by several serotypes. It is more difficult to be certain that the two episodes of rotavirus infection in hospital shown by baby 17 are truly separate. The positive stools were obtained at least 15 days apart with seven stools negative for rotavirus between them, and six of these stools contain other viruses. Consequently we believe these episodes to be separate, and such multiple episodes have been observed with rotaviruses (3 babies), caliciviruses (2 babies) and adenoviruses (10 babies).

Most of the 33 serotypes of adenovirus have been isolated from stools in cell culture and double isolations from the same stool have been found (E. J. Bell, personal communication). With so many serotypes, multiple episodes might be expected to be more common with this virus, as was found in this study. With only small amounts of crude stool extract available, typing of individual recognizates by immune electron microscopy was not possible. As shown in Table 2, there were 45 episodes, with 5 the highest number to be observed in one baby. In this study adenoviruses seemed to occur at random in stools and there is no good evidence to link them with disease, though an association has been described by Flewett *et al.* (1975) and Whitelaw, Davies & Parry (1977). From our results, it seems likely that most, and maybe all, babies would be found to excrete adenoviruses at one time or another if enough stool specimens are examined.

Viruses of all kinds were found more frequently in the stools of babies with diarrhoea though no one virus predominated. This result would be consistent with a hypothesis that some of the babies had a greater propensity for diarrhoea which then flushed out any viruses present in the gut. As Cameron *et al.* (1978) have commented, not all authors have defined clearly what they call diarrhoea. This is a condition for which there are no clearly objective criteria, nor can there be. All babies have occasional loose stools, and, as Fig. 3 shows, it can be difficult to distinguish the trivial episode from the serious except by a subjective, and often retrospective, assessment. It is not easy to elicit a history of the child's normal bowel habit, particularly when it may be too young to have established one, yet this 'normality' is the background against which an alteration in bowel habit must be seen. Compared with the serious life-threatening diarrhoea seen in undernourished children in the tropics none of our patients was seriously ill, and

none of the viruses we observed caused severe illness in these babies. Some babies had frequent, loose or watery stools and we found more viruses in these stools. Whether such infants were more susceptible to *any* virus invading the gut is not known; nor is it known whether such invasion precipitated diarrhoea. From our results it is difficult to define either a rotavirus disease entity (Walker-Smith, 1978; Flewett & Woode, 1978) or the role of any virus in infantile diarrhoea. The results, and dilemmas posed by them, are similar to those found by Bolivar *et al.* (1978) in Mexico in adults. They looked only for rotaviruses but found that only visitors appeared to develop diarrhoea in temporal association with virus. It seems possible that some babies have a gut whose equilibrium is more easily disturbed by insults which may include viruses as well as bacteria, inappropriate feeding or other factors at present unknown. In hospital, frequent changes in the type and amount of faecal virus excreted by babies in the wards have been detected, and this suggests cross-infection. Some evidence for this possibility has been published (von Bonsdorff *et al.* 1976; Chrystie, Totterdell & Banatvala, 1978) but more knowledge is needed about how it occurs and how these viruses are transmitted in the community.

These surveillance data, though representing considerable work, cannot pretend to uncover the full picture of the patterns of virus infection in these babies. Even so they suggest that the patterns are complex. They may be unique to the housing area that we investigated, or even to Glasgow though this seems unlikely, and it will be necessary to repeat this kind of investigation to confirm that they are not unique. If they are shown to be a general phenomenon then it will be the background against which the need for and effectiveness of any vaccines can be measured. So far we have detected the presence of an iceberg the size and extent of which we have yet to chart.

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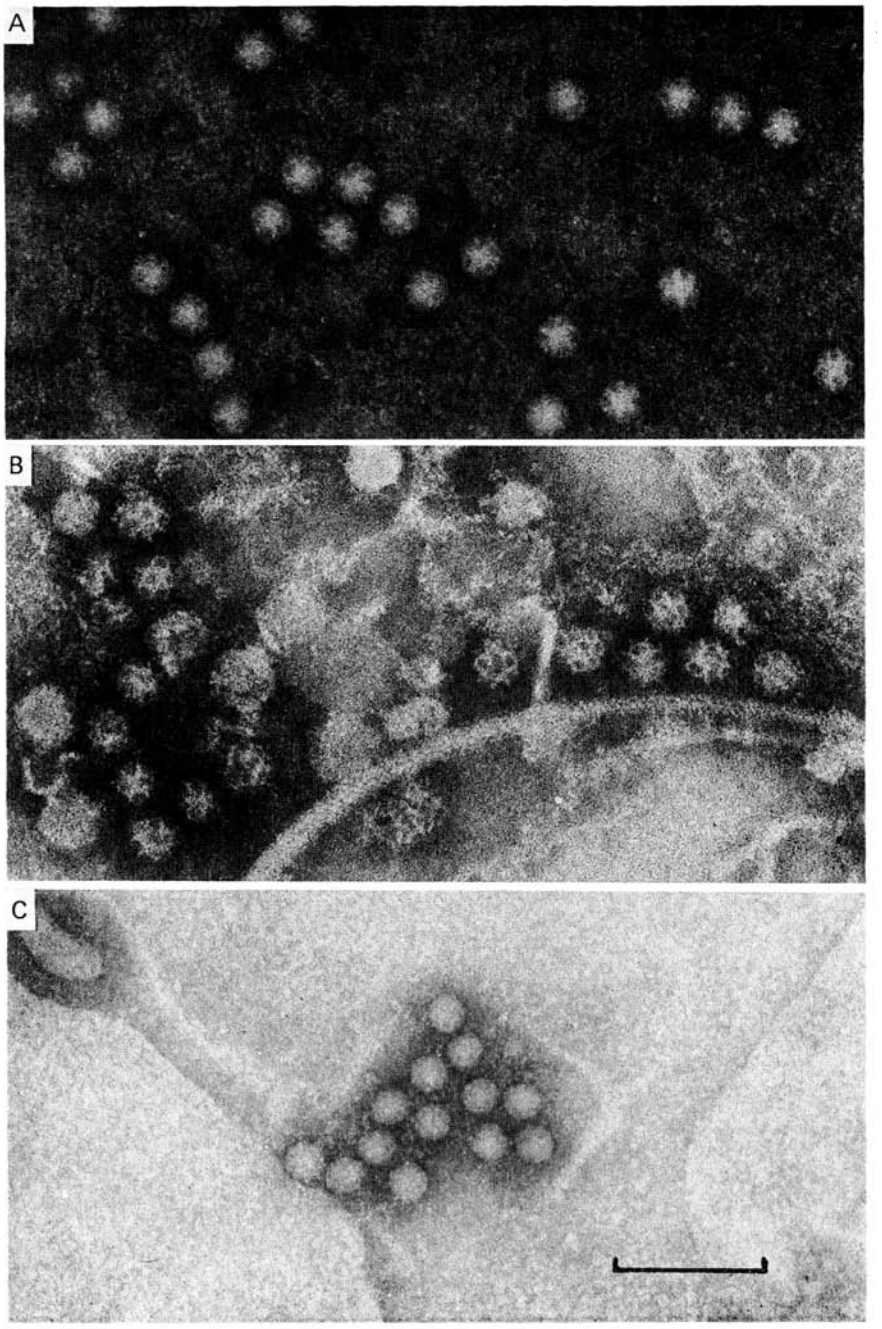

T. M. SCOTT AND OTHERS

(*Facing p.* 485)

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EXPLANATION OF PLATE

Plate 1

Viruses seen in stool specimens. Negatively stained by 3% potassium phosphotungstate pH 7·0, and printed at a final magnification of 200000×. (*A*) Astrovirus. (*B*) Calicivirus. (*C*) Small round virus. Scale bar = 100 nm.