

Epidemic of echovirus 19 in the north-east of England

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SUMMARY

We report the first large-scale outbreak of echovirus 19 infection. It occurred in the north-east of England during the summer and autumn of 1974. The virus was isolated from 268 patients in the region. The infection spread from the urban to more rural areas, reaching a peak in mid-August. Males were affected more often than females in the ratio 1.6:1. Half of the patients were under eight years of age, relatively few were over 35 years. Aseptic meningitis and upper respiratory infections were the commonest presentations, though a wide range of other diseases occurred including gastroenteritis, myalgia, pericarditis, undifferentiated pyrexia, rashes and a syndrome analogous to bacteraemic shock. There was no evidence that the pattern or severity of the disease changed during the outbreak. Infants under the age of six months were more seriously affected than older children and adults. All patients except one made an uneventful recovery. Of the routine tissue culture cells HEp2 and HeLa were by far the most satisfactory for virus isolation.

INTRODUCTION

Since the recovery of the prototype strain of echovirus type 19 from the faeces of an infant with diarrhoea by Ramos-Alvarez & Sabin (1958), only occasional reports of further isolations have appeared in the literature. A recent report (Assaad & Cockburn, 1972) analysing the world-wide returns for enterovirus isolations, other than poliovirus, to the World Health Organization, fails to mention echovirus type 19 at all. The minimum requirement for inclusion in this report was 25 isolations from one laboratory in one year, indicating that echovirus 19 has not previously been a significant cause of illness. Two groups have reported series of 30 (Cramblett *et al.* 1962) and eight (Crovari, Chiossi & Vannucci, 1969) patients infected with echovirus 19, whose main symptoms were respiratory, while a third report has associated this virus with a fatal illness in three infants (Philip & Larson, 1973).

During the summer of 1974 a large outbreak of echovirus type 19 infection occurred in the north-east of England. The first isolations of echovirus 19 were made in October 1973 and a total of 12 sporadic cases were seen up to the middle of May 1974. From then until the end of November a major epidemic occurred,

with virus being isolated from 268 patients. This report describes the clinical features and epidemiology of the outbreak. The virological examinations were carried out both at the Public Health Laboratory, Newcastle General Hospital and the Department of Virology, Royal Victoria Infirmary.

MATERIALS AND METHODS

Patients

When it became clear that a widespread outbreak of echovirus 19 was in progress a standard form was designed for the collection of clinical data from all patients from whom virus was isolated. Information concerning those patients admitted to hospitals outside Newcastle upon Tyne and non-hospitalized individuals was obtained from general practitioners, physicians and pathologists who kindly completed and returned the standard forms. The data on patients admitted to hospitals in Newcastle upon Tyne were collected from their case records by the investigating team.

Specimens

The number of specimens received for virus isolation depended both on the type of illness and whether or not the patient was in hospital. Cough swabs were obtained from all patients with respiratory symptoms, while nasopharyngeal secretions (NPS) were also collected from most of the children. Specimens of C.S.F. were submitted from most of those with central nervous system (C.N.S.) involvement, while faeces were sent to the laboratories from a wide range of patients. The method of carriage of the specimens to the laboratory ranged from immediate delivery on ice to over 24 hr. in the post. Before inoculation, extracts of nasopharyngeal secretions, faeces and swabs were made in Hanks's balanced salt solution with 0.25 % bovine plasma albumin and antibiotics, but specimens of C.S.F. were inoculated without treatment.

Cell lines

Specimens from the respiratory tract were inoculated on HEp2, Bristol HeLa, WI-38 and RMK. Faeces and C.S.F. specimens were inoculated on HEp2, Bristol HeLa and RMK, a few specimens were inoculated on Vero cells. Blind passages were carried out as required. Virus identification was by neutralization tests using the echovirus diagnostic sera supplied by the Standards Laboratory for Serological Reagents, Central Public Health Laboratory, Colindale.

RESULTS

Distribution of epidemic

The virus became established in the community during the second half of May and lasted until the third week in November, a total of 28 weeks. The frequency distribution was determined by taking the date of receipt of the first specimen from each patient at the testing laboratory in lieu of the date of onset of illness, and then allocating the individuals to one of fourteen two-week periods. Fig. 1

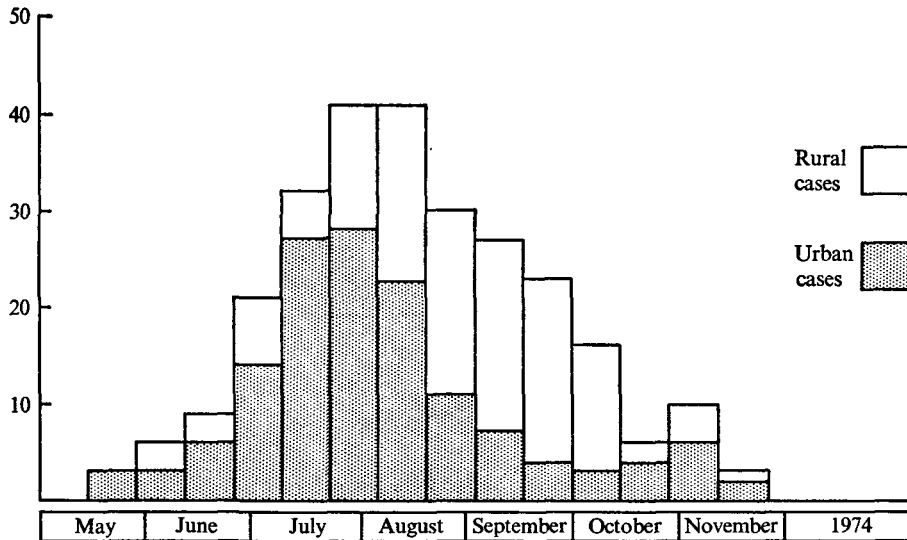


Fig. 1. Frequency distribution of urban and rural cases.

shows the number of infections in each time interval, in both urban and rural areas; the former predominated during the first half of the epidemic.

The geographical distribution of the cases within the region is shown in Fig. 2. Although the clinical picture presented by the 12 pre-epidemic patients did not differ significantly from those observed during the epidemic, they were excluded from the main analysis. Most of the cases occurred in the major conurbation, with 75 in Newcastle and 42 in Gateshead. However, virus was isolated from patients as far apart as Wooler in the north and Hartlepool in the south. Absence or paucity of isolations from certain population centres may be attributed either to their lying outside the catchment area of the testing laboratories, to failure to refer specimens from all the patients, or to the virus not reaching these areas.

Fig. 3 shows the age and distribution of the infected persons. The age range was from 14 days to 46 years, with 50% of the patients less than eight years of age. The number of cases, calculated per year of age for each group, was highest for children under two years and remained at a lower constant level to age 35, after which infection became relatively uncommon. There was a preponderance of males to females in each of the age groups, 62% males and 38% females overall.

Clinical picture

Tables 1 and 2 show the main patterns of illness and the clinical features associated with echovirus 19 infection in each age group. The illness lasted from 3 to 16 days and most commonly affected the upper respiratory tract, the meninges or both. It also sometimes affected the skin, the gastro-intestinal tract, and occasionally skeletal muscle. In two cases the pericardium was involved. There was no evidence that any of the patients suffered from myocarditis, encephalitis, or from disease of the renal, hepatic, lower respiratory and reticulo-endothelial systems.

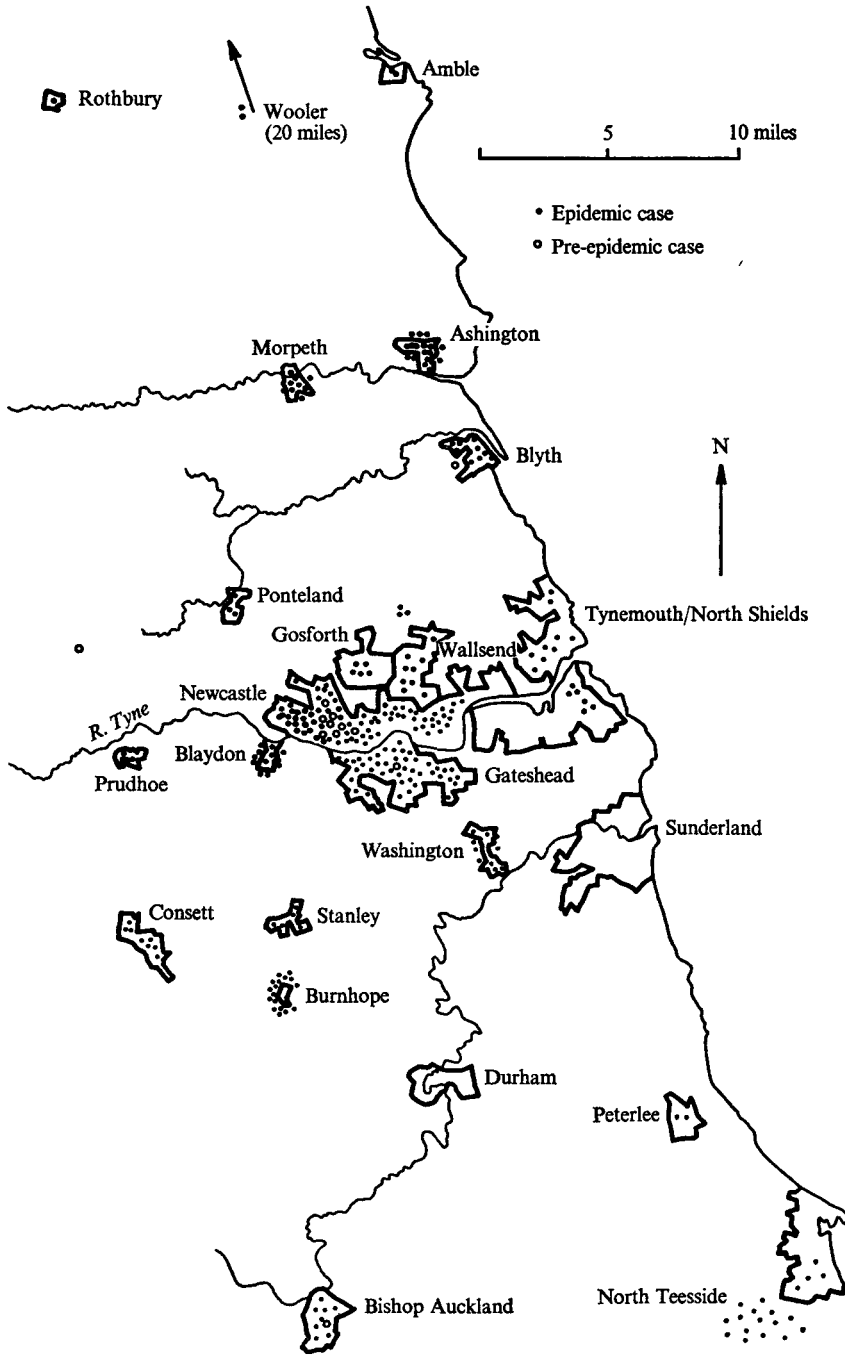


Fig. 2. Geographical distribution of cases.

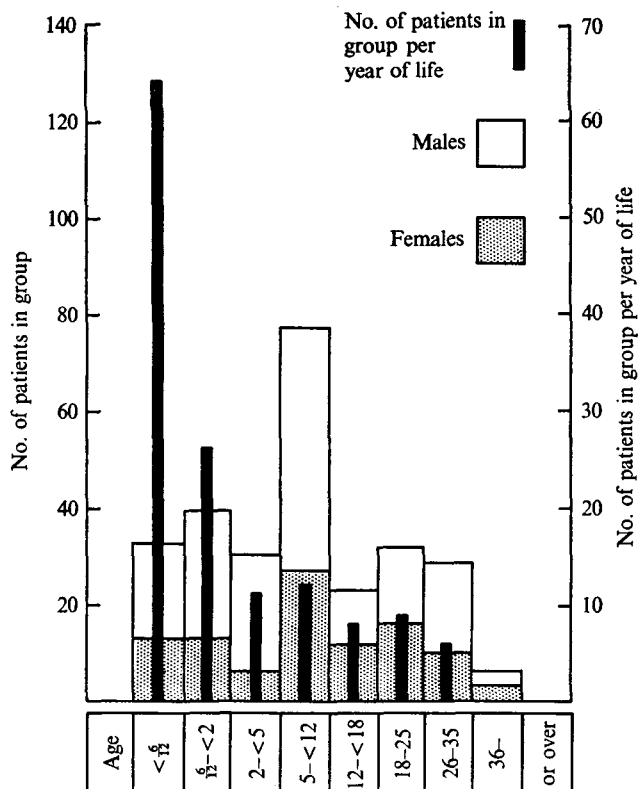


Fig. 3. Age/sex distribution of cases. The solid black columns indicate the number of patients in group per year of life, and are measured on the right-hand scale.

Most patients were pyrexial, with maximum temperatures usually about 39°C . and reaching 41°C . in a few instances. Where no pyrexia was recorded it may well have been present before admission to hospital. Persons presenting only with fever and malaise were classified as pyrexia of unknown origin. Patients were regarded as having meningitis when the C.S.F. contained more than 10 white cells/mm.³, yielded echovirus 19 on culture, or both. Meningism was the most frequent cause of hospital admission for adults and children over the age of five. Virtually all patients in this group complained of headache, vomiting and neck stiffness, and often older children and adults of photophobia as well. In some patients drowsiness and a positive Kernig's sign were noted. Meningitis was common in infants under six months although the signs were less specific. The anterior fontanelle usually felt normal although it was occasionally recorded as being full but not bulging.

Upper respiratory tract infection occurred frequently, particularly in the younger patients between the ages of six months and five years, and was the commonest presentation. In most cases the infection appeared to be a non-exudative pharyngitis, with or without tonsillitis, causing many of the older children and adults to complain of sore throat. In younger children otitis media was also common with the tympanic membranes injected but not distended. A proportion of those in each age group had coryza. Though a few small children were recorded as having

Table 1. *Percentage distribution of clinical syndrome by age*

Syndrome	6/12-						
	< 6/12	< 2	2- < 5	5- < 12	12- < 18	18-25	26+
Meningitis	21	5	18	49	50	46	68
U.R.T.I.	14	58	36	20	21	7	3
Gastroenteritis	12	3	—	—	—	—	3
Bornholm's	—	—	7	3	—	4	12
Viraemic shock	3	—	—	—	—	—	—
P.U.O.	9	8	11	11	4	4	9
Meningitis + U.R.T.I.	15	—	18	15	25	32	3
Meningitis + viraemic shock	6	—	—	—	—	—	—
Gastroenteritis + viraemic shock	6	—	—	—	—	—	—
Meningitis + gastroenteritis	6	—	—	—	—	—	—
U.R.T.I. + gastroenteritis	3	21	—	3	—	—	—
U.R.T.I. + L.R.T.I.	—	3	7	—	—	—	—
L.R.T.I. + gastroenteritis	—	3	—	—	—	—	—
Incidental*	—	3	7	3	—	7	—

* Includes 3.6% (2 cases) of pericarditis.

Table 2. *Percentage positive clinical features by age*

Clinical features	6/12-						
	< 6/12	< 2	2- < 5	5- < 12	12- < 18	18-25	26+
Coryza	16	31	10	3	13	6	6
Influenza	6	—	7	8	9	16	17
Sore throat	34	54	97	47	39	34	9
Otitis media	16	44	23	5	4	—	—
Chest pain	—	—	—	4	9	25	31
Muscle pain	—	—	—	7	9	31	29
Pericarditis	—	—	—	—	6	—	—
Convulsions	3	51	40	4	—	—	—
Headache	—	—	33	81	87	75	74
Photophobia	—	—	3	25	57	63	43
Meningism	28	5	20	62	87	66	54
Vomiting	25	31	37	68	61	53	43
Kernig's	6	—	3	34	35	31	23
Drowsiness	19	—	3	13	9	9	3
Abdominal pains	3	3	27	38	13	9	3
Diarrhoea	34	26	7	7	—	9	9
Pyrexia	94	72	100	88	87	66	71
Lymphadenopathy	13	31	20	30	17	3	3
Rash	50	15	7	1	4	—	3
Number in group	32	39	30	77	23	32	35

bronchitis no clinical signs or radiographic evidence was obtained to confirm a diagnosis of lower respiratory tract infection. Almost half of the children in the six months to five years age group had febrile convulsions and this was the main reason for admission to hospital

Gastroenteritis was regarded as present when there was diarrhoea with or without vomiting. It occurred most frequently in infants, usually in combination

with respiratory or meningeal involvement. The stools were sometimes green and usually very loose although never profuse enough to cause serious dehydration.

Abdominal pain occurred frequently in children between two and 12 years of age, and less often in older patients. It was associated with respiratory and meningeal infections rather than with gastroenteritis and was typically a constant pain of moderate severity in the centre of the abdomen. There was no tenderness or enlargement of the liver and spleen.

About half the adults and a few older children complained of aching muscles. Some thought that the illness felt just like influenza. Others complained of chest pain of a muscular nature and when this was the dominant symptom the patient was regarded as having a Bornholm-like disease. In no case was any weakness of the muscles or pain in the joints recorded. In a few instances the nature of the chest pain suggested the possibility of pericarditis. This was confirmed in two patients on the basis of ECG changes. In one a friction rub was also heard.

A rash was present in half the children under six months and in a few of the older children and adults. It usually consisted of discrete erythematous macules or maculo-papules from 1 to 5 mm. in diameter, sometimes spreading to form confluent areas. The rash appeared on the second or third day of the illness, first on the face and upper trunk, sometimes spreading later to the limbs, and faded after about 4 days.

In infants echovirus 19 produced its most diverse and severe manifestations, often affecting more than one system. The onset of illness was insidious, with fever, irritability and reluctance to feed. In five babies, all less than three months old, there was rapid deterioration to a state of peripheral circulatory failure and hypotonia which we think might be aptly termed 'viraemic shock'. When rash was present this condition was indistinguishable from septicaemia. The C.S.F. from all five babies was examined and two proved to have aseptic meningitis. Two others had diarrhoea. All remained severely ill for two to three days but made a complete recovery.

Morbidity

The youngest child in the survey, a female baby of 14 days, was the only patient who died. Echovirus 19 was isolated from her C.S.F. but she also had severe endocardial cushion defect and therefore the infection was considered to be only a contributory factor rather than the actual cause of death. Serious illness occurred in eight patients (3%), all but one of whom were under six months of age. The majority of the patients (66%) were considered to have an illness of moderate severity and 31% a mild illness. All made uneventful recoveries without any suggestion of residual disability.

Retrospective attempts to obtain information on the contact history of the hospital patients were frustrated by the lack of such details in the case notes. Very few isolations of echovirus 19 were made from two members of the same family. On one occasion two friends, the only confirmed cases from a country town, were admitted within a few days of each other.

Table 3. *C.S.F. findings*

Virus culture	White cell count/mm. ³				Protein (mg./100 ml.)		No. in group
	< 10	10-50	50-200	200+	< 50	> 50	
Positive	26	27	23	12	68	20	88
Negative	8	2	4	2	10	6	16
Not received for culture	12	14	17	4	39	8	47

Table 4. *Results of isolation attempts on 278 specimens known to contain ECHO virus Type 19 collected from 167 patients*

Cell line	HeLa	HEp2	WI-38	RMK	VERO
Number tested	94	241	206	264	92
Number virus isolated	82	235	115	105	15
Mean time for isolation (days)	7.1	8.0	7.3	10.0	15.9

Laboratory investigations

Routine haematological tests (haemoglobin, white blood cell, film and differential count) were performed on most patients and were found to be normal. The ESR, however, when performed, was usually moderately elevated.

Lumbar punctures were performed on 151 patients in the series and 104 samples of C.S.F. were cultured for virus. Echovirus 19 was recovered from 88, making an isolation rate of 85%. Table 3 shows the cell counts and protein concentrations in relation to virus isolation. Although the group from which virus was not isolated was small, there was no indication of a substantial difference in cell counts or protein concentrations compared with the virus positive group. Protein concentrations in the C.S.F. were raised in a few specimens, while cell counts were within the normal range in many, including 26 from which virus was isolated. Analysis of the differential count was restricted to those patients whose total C.S.F. cell counts were greater than 50/mm.³. Great variations were observed, but two-thirds of the patients showed a predominantly polymorphonuclear response. All C.S.F. glucose concentrations were found to be within the normal range.

The results from both laboratories confirmed that RMK cells were not as suitable for the isolation of echovirus 19 as the continuous cell lines of human origin such as HeLa and HEp2 which were very much more sensitive. The analysis of the results from 278 specimens containing echovirus 19 is given in Table 4. The lower sensitivity of the RMK and Vero cells is shown by the poor rates of isolation (39.8% for RMK and 16% for Vero) and the extended times required for isolation of the virus. The isolation rate on HEp2 cells was significantly higher than on HeLa ($\chi^2 = 14.4$, $P < 0.005$), although the time required for isolation was only one day longer. The isolation rate on WI-38 cells (55.8%) was probably too low, as the tubes were discarded in at least 22 instances before the virus was isolated on any other cell line. All strains of virus isolated during the epidemic were neutralized without difficulty. Nineteen strains were tested for mouse pathogenicity, six tissue culture fluids from C.S.F. specimens, two tissue culture fluids from NPS specimens

and 11 faecal extracts. All were completely non-pathogenic for newborn mice and neither laboratory was successful in adapting any of the strains on passage.

Management of patients

A great variety of different drugs was given to patients infected with echovirus 19. Thirty per cent of all patients received antibiotics, in most instances to cover the possibility of bacterial meningitis. Sulphonamides, penicillin and chloramphenicol were the agents most frequently used. All of the eight seriously ill patients received intravenous fluids as well, since they initially appeared to have septicaemic shock. Many children were given paracetamol both for its analgesic and anti-pyretic effects. Some adults were given more powerful analgesics, often to relieve severe headache or occasionally chest and muscle pain. Where vomiting was a problem anti-emetics were prescribed for short periods.

DISCUSSION

The frequency distribution of the cases over the summer and autumn, with the peak occurring during the first half of August, was typical of an enterovirus outbreak. Similarly the occurrence of isolated, sporadic cases from the autumn of the previous year was also typical of enterovirus epidemics. However, there was no reason at the time to suspect that a widespread epidemic would occur, as echovirus 19 had never previously been associated with a major outbreak of clinical illness. The infection appeared to spread slowly from the metropolitan area to the surrounding rural areas where it reached a peak four weeks after the urban epidemic, although urban cases continued to occur to the end of the outbreak. Isolations of echovirus 19 in other parts of Great Britain were relatively infrequent during the main period of the outbreak in the north-east, but became more frequent and widely distributed towards the end. It would therefore seem likely that other regions of the country might experience large-scale epidemics during the summer and autumn of this year, 1975.*

In order to determine whether the pattern of the disease changed during the course of the epidemic, the cases occurring during the first half were analysed separately from those occurring during the second half. Apart from a larger number of cases in the 5–12 years age group during the first half of the epidemic, no differences were found in the age or sex distribution, clinical features, or severity of the disease between the two halves of the outbreak. The single anomaly can be explained on the basis of a reduction in the infection rates consequent upon the schools closing for the summer vacation. An unexplained preponderance of males to females has been reported for other echoviruses (Melnick, 1965). In this outbreak the ratio was 1.6:1, and as the severity of illness was the same for both sexes it could not be explained on the basis of greater concern being shown for male patients.

The clinical picture presented by patients infected with echovirus 19 varied with age. The most common syndrome in all patients over five years of age was

* See note at end of paper.

aseptic meningitis, sometimes with a sore throat or abdominal pain. In children from six months to five years the typical symptom was pharyngitis, often with febrile convulsions. Meningitis was much less common in this age range, and of the few children with frank meningitis, several were verging on the adjacent age ranges. The pattern of these illnesses is similar to that observed in outbreaks caused by echovirus types 4, 6, 7, 9, 11, 16 and 30 (Melnick, 1965), although the high incidence of febrile convulsions in pre-school children does not appear to have been previously recorded. Earlier reports had associated echovirus 19 with sporadic cases and small outbreaks of upper respiratory tract infections, bronchitis, gastroenteritis and meningitis (Cramblett *et al.* 1962; Crovari *et al.* 1969; Faulkner & Ozere, 1960), but never before with such a massive and varied epidemic.

One unique feature of this outbreak was the very high incidence of infection in infants under six months of age. Philip & Larson (1973) reported three neonates who died from hepatic necrosis and massive terminal haemorrhage due to overwhelming infection with echovirus 19. In this epidemic the manifestations in infants under six months varied, frequently including a rash, often with meningitis, and sometimes presenting as a severe illness similar to septicaemia, which we have called 'viraemic shock'. No cases similar to those described by Philip & Larson were recorded.

The proportion of these infants found to have meningeal involvement might have been even greater if all C.S.F. specimens had been submitted to the testing laboratories. Nevertheless, the high isolation rate from C.S.F.s was a feature of the outbreak. Cell counts in the C.S.F.s contrasted with the generally accepted criteria for discrimination between meningism and meningitis on the one hand and between bacterial and viral meningitis on the other, since 30% of the C.S.F.s with normal counts were virus positive and 66% of the samples with total counts sufficiently high to allow a reliable differential count showed a predominantly polymorphonuclear response.

The high incidence of upper respiratory tract symptoms coupled with the frequent isolation of virus from respiratory secretions suggests that spread by this route was a more important feature of this outbreak than is usually seen in enterovirus epidemics. A retrospective examination of some of the stored NPS by the indirect fluorescent antibody technique, using a suitable rabbit antiserum prepared against echovirus 19, indicated that this method could be helpful in providing a rapid diagnosis should this virus be found in other areas in epidemic form.

Problems arose in the management of some patients as, in the face of an epidemic of this size, with large numbers being admitted with the septicaemic and meningitic picture, sometimes indistinguishable from meningococcal septicaemia, there was a real danger that a sporadic case of bacterial infection might be missed at first. Unfortunately this did occur in one instance and antibiotic treatment was delayed.

We should like to express our thanks to the many physicians, pathologists and general practitioners throughout the region who referred material to us, gave access to case records, and supplied information; and to the technical and scientific staffs of the two laboratories.

Note added in proof. During 1975 large outbreaks of echovirus infections occurred in the rest of the country, particularly in the Midland region. Over 1500 isolations were reported to the *Communicable Disease Report* of the P.H.L.S. Age, sex and seasonal distributions and main clinical features were similar to our own findings.

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