Role of viruses in febrile convulsions

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SUMMARY A disseminated viral illness was demonstrated by isolating a virus from the CSF, blood, or urine in 27% of 73 children who were admitted to hospital after a first febrile convulsion. However, a viral aetiology could be implicated for 86% of the children after combining results of tissue culture, electron microscopy, mouse inoculation, complement fixation tests, and interferon assay. Parallel bacterial cultures showed a possible pathogen in 29% of children, but in only 4% was the pathogen isolated from the CSF, blood, or urine. No correlation was found between the nature of the pathogen (or evidence of its dissemination) and the severity of the convulsion, degree of fever, CSF protein, CSF white cells, or the WBC. The results suggest that a febrile convulsion could be a response to invasion of the blood stream or central nervous system by a micro-organism which is usually a virus. Invasion may be of such brief duration that successful isolation of the virus from the blood, CSF, or urine is not more commonly achieved.

Between ages 6 months and 5 years about 3% of all children suffer at least one convulsion in association with a febrile illness (Lennox-Buchtal, 1973; Nelson and Ellenberg, 1978). There is now greater understanding of the chemical and structural characteristics of the immature brain and of the role of pyrogens in the pathogenesis of fever, but no direct link has been discovered between the febrile and the convulsive state (Lennox, 1953; Ounsted, 1976a). It has been suggested that the convulsion depends on the nature of the infecting micro-organism in combination with fever, age, and genetic predisposition. Epidemiological studies from western Europe and the USA suggest that febrile convulsions are associated with upper respiratory tract infections and other illnesses which are assumed to be due to viruses (Miller *et al.*, 1960; Millichap, 1968; Lennox-Buchtal, 1973). Even if there is no convulsion, viral illnesses can produce abnormal neurological signs, and slowing of the EEG pattern, without detectable changes in the CSF (Wallace and Zealley, 1970). The febrile convulsion might be a cerebral manifestation

of a generalised viral illness or even a direct effect of virus on the central nervous system.

In a study from Nigeria about half the cases of febrile convulsions were associated with malaria parasitaemia, but enteroviruses were isolated from the blood or CSF in 8 out of 105 children on whom virus isolation tests were performed (Familusi and Sinnette, 1971; Familusi *et al.*, 1972). Most other reports of the viruses identified in association with febrile convulsions have been limited to isolates from the throat or faeces or to serological tests (Wallace and Zealley, 1970; Stokes *et al.*, 1977). The aim of this study was to establish a viral diagnosis and to find viruses in the CSF, blood, or urine immediately after the convulsion.

Patients and methods

The study lasted from 1 November 1976 to 1 December 1977. The patients were between ages 6 months and 5 years and were admitted with a generalised or focal convulsion associated with a rectal temperature of at least 38°C recorded in hospital within 24 hours of the convulsion. None of the children had had a previous convulsion.

Every child was seen within 24 hours by the same clinician, who recorded, on a standard proforma, the medical and developmental history, the findings on examination, and a clinical diagnosis of the illness which accompanied the convulsion. Each patient was reviewed daily in hospital and again in out-patients department 3 weeks later.

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Virological methods. Viral infections were detected by inoculation of tissue cultures, intracerebral inoculation of suckling mice for Coxsackie A viruses, electron microscopy for rotavirus, complement fixation tests, and interferon assay.

For viral cultures each prepared specimen was inoculated on to human embryonic lung fibroblasts (MRC5), Ohio HeLa cells, and secondary monkey kidney cells (Lewis *et al.*, 1979). CSF and heparinised blood were immediately inoculated into the tissue cultures and incubated in the treatment room where lumbar puncture and venepuncture were performed. Throat swabs in viral transport medium were kept at 4°C, and within 2 hours most were inoculated into tissue culture. Nasopharyngeal secretions were collected, as well as throat swabs, from 28 patients who entered the study after May 1977. Urine and stool specimens which could not be inoculated within 2 hours were stored at -70°C until inoculation. Faeces were suspended in nutrient broth, clarified by centrifugation, and the final supernatant was used for tissue culture, electron microscopy (Lewis *et al.*, 1979), and mouse inoculation.

Faecal specimens were screened for Coxsackie A viruses by intracerebral inoculation of litters of suckling mice on their first day of life (Melnick *et al.*, 1969). Throat swabs or nasopharyngeal secretions were used to screen those patients from whom no stools were obtained. When a screening specimen was positive all available specimens from other sites of that patient were examined.

Serological tests were performed on serum which was collected on admission, and again after an interval of 3 to 4 weeks. Complement fixation tests (CFTs) were performed against the following antigens: influenza A, influenza B, adenovirus, psittacosis, coxiella, measles, respiratory syncytial virus (RSV), *Mycoplasma pneumoniae*, mumps, herpes zoster, herpes simplex, Coxsackie B, cytomegalovirus, and parainfluenza 1, 2, and 3. Antibodies to rubella were sought by haemagglutination inhibition. All convalescent sera were screened; acute phase sera were only tested if a titre of 1/20 or higher was obtained. Results were regarded as positive if there was at least a 4-fold rise in titre between acute and convalescent sera.

The interferon activity of serum collected within 2 hours of admission was assayed by a plaque inhibition technique, on a semimicro scale, using continuous vervet monkey kidney cells in wells in plastic (Matthews and Lawrence, 1979). The serum was diluted 1:10 and left on the cell sheet for 24 hours at 37°C in a humid atmosphere containing 5% carbon dioxide. The monolayers were washed and vesicular stomatitis virus was added as the challenge virus.

A reduction of at least 50% in the mean plaque count was taken as indicating the presence of interferon. Dilutions of the MRC Research Standard B (69/19) for human interferon were included with each test, and 1 unit of this was found to give between 50 and 70% reduction.

Bacteriological methods. CSF was sent to the microbiology department for immediate microscopy and culture. Blood was incubated at 37°C in glucose broth and thioglycollate, subcultures were made aerobically and anaerobically. Throat swabs were taken on serum-coated wool buds. In the first part of the study they were transported in Stewart's medium and plated within 4 hours. From July 1977 all throat swabs were taken by the same clinician, who plated them immediately on to blood and chocolate agar. Colonies were identified by standard techniques and all β -haemolytic streptococci were grouped serologically. Urine specimens were inoculated on to CLED medium within 4 hours of collection. Colonies were enumerated and identified by standard techniques. A significant growth was taken as $>10^8$ organisms/litre. Fresh stool specimens were plated on to deoxycholate agar and MacConkey agar and inoculated into selenite broth. Enteropathogenic *Escherichia coli* were identified by using antisera to 15 recognised enteropathogenic types (PHL Colindale). From April 1977 a selective medium was used to isolate campylobacter species (Skirrow, 1977).

Additional tests were WBC of the peripheral blood, plasma glucose level, and CSF protein and glucose concentrations.

Results

37 boys and 36 girls were studied. The mean age was 18.9 months and only 3 (4%) children were over 3 years. Two children were excluded because virological investigation had been omitted; one had meningitis, with *Haemophilus influenzae* cultured from the blood and CSF; the other child had clinical measles. All other patients admitted during the study period were retained, although a complete set of microbiological specimens was not obtained from every patient; there was sometimes insufficient serum for interferon assay and a few patients did not return for convalescent serology.

Virology results. A virus was identified from at least one site in 46 (63%) out of 73 patients. The viruses are named in Table 1; from 9 patients, viruses of more than one type were identified.

There was a significant rise in antibody titre in 14 (20%) out of 69 patients. All had a 4-fold response

Table 1 Results of virus isolation tests with clinical diagnoses. (Number of patients in parentheses)

Type of virus	Clinical diagnosis
Enterovirus (17):	
Echovirus (5)	Tonsillitis (1), pharyngitis (1), otitis media (1), URTI (1), PUO (1)
type 3 (3), 5 (1), 22 (1)	
Coxsackie A (7)	Tonsillitis (2), pharyngitis (2), URTI with conjunctivitis (1), measles (1), PUO (1)
type 2 (1), 4 (1), 10 (5)	
Coxsackie B (3)	Pharyngitis (1), PUO (1), gastroenteritis with orchitis (1)
type 1 (1), 2 (1), 3 (1)	
Poliovirus type 3 (1)	Measles vaccine*
Enterovirus (EM only) (1)	Otitis media with gastroenteritis†
Adenovirus (22)	Tonsillitis (4), pharyngitis (1), otitis media (9), URTI (3), tonsillitis with gastroenteritis (1), otitis with gastroenteritis† (1), URTI with gastroenteritis (1), dysentery (1)‡, meningitis (1)§
type 1 (6), 2 (12), 3 (1), 5 (1)	
type 1 with 3 (1), CFT only (1)	
Influenza B (1)	URT
Parainfluenza (7)	Tonsillitis (2), pharyngitis (1), otitis media (1), croup with otitis (1), URTI (2)
type 1 (1), 2 (1), 3 (5)	
Measles (3)	Measles (4), measles vaccine (1)*
Measles CFT (2)	
Respiratory syncytial virus (2) serology only	
Rhinovirus (2)	Measles (1), tonsillitis (1)
Cytomegalovirus (4)	URT (1), meningitis§ (1)
Rotavirus (EM only) (2)	Tonsillitis (1), otitis media (3)
	Gastroenteritis (1), otitis media with gastroenteritis (1)†

*Case 39 (see Table 2), †Case 23, ‡Case 75 (see Table 3), §Case 59 (see Table 2).

except one, with doubling of an initially high titre; from 11 of these patients a virus of the same type was isolated by tissue culture. A rise in antibody titre to RSV was demonstrated in 2 cases, but the virus was not isolated; in addition one of these patients was shown to be infected with an adenovirus by CFT and culture, and the other also had a positive measles CFT.

Interferon was detected in the serum of 31 (47%) out of 66 patients. From 16 of these a virus was isolated; there was no other evidence of a viral illness for the remaining 15 patients.

63 (86%) out of 73 patients had some evidence of a viral illness when all the methods were considered together—that is tissue culture, electron microscopy, mouse inoculation, serology, and interferon assay.

Evidence of a systemic viral illness was demonstrated in 20 (27%) cases by isolating a virus from the CSF, blood, or urine. A virus was isolated from the CSF of 4 patients, from the blood of 12, and from the urine of 13 patients (Table 2).

Bacteriology results. Pathogenic bacteria were isolated from 21 (29%) patients, Table 3. There was no difference in the isolation rate when throat swabs were plated immediately rather than transported in Stewart's medium.

A systemic bacterial illness was demonstrated in

3 (4%) cases. From one patient *H. influenzae* was isolated from the blood and CSF. Two patients had a significant *E. coli* bacteriuria, which was confirmed on subsequent specimens. From 14 of the patients with a bacterial isolation a virus was also recovered.

Interferon was detected in 9 cases with a bacterial isolation but a virus was also recovered from 5 of these.

Other investigations. The patient with *H. influenzae* meningitis had a high CSF WBC and a high CSF protein level; of the rest only one patient had more than 4/mm³ white cells in the CSF, and one had a CSF protein >0.4 g/l (40 mg/100 ml). There was no relationship between the CSF findings and the nature of the pathogen, or evidence of viral dissemination.

The WBC did not distinguish those with bacterial isolations from those with viral isolations. However, a group of patients from whom adenoviruses were identified had significantly higher white cell counts than any others, i.e. 80% of patients with adenovirus isolations had >15 000/ml (mainly polymorphs) compared with 36% of patients without adenovirus ($\chi^2 = 9.8$, $P < 0.01$).

Clinical data

From the histories given by the parents perinatal asphyxia may have occurred in 6 cases. Later in the first year of life one infant had an asphyxial episode but the others had an unremarkable medical history. The probability of normal developmental achievement before the convulsion was indicated by asking the mothers the ages at which their children had achieved four major milestones (Neligan and Prudham, 1969). 66 (90%) children had reached all four milestones by the ages expected for 90% of children of their own sex, and no child failed more than one milestone. Thus the developmental achievements of the group were no different from those of the general population. We therefore cannot verify that perinatal problems and abnormal development are commonly found in children suffering febrile convulsions (Millichap, 1968; Wallace, 1972, 1975). A parent or sibling of 8 (11%) of our children was known to have suffered from febrile convulsions and a further 6 (8%) had each suffered at least one convulsion which was not associated with fever.

The mean length of illness before the convulsion was 13.4 hours (range 0 to 96). The symptoms noted by the parents were nonspecific: irritability, anorexia, and fever were commonly recorded but cough, vomiting, or diarrhoea sometimes indicated the likely site of infection.

Table 2 Details of patients with viruses isolated from CSF, blood, or urine

Virus	Case	CSF	Blood	Urine	Throat swab	Naso-pharyngeal secretions	Stool	Serology	Other viruses	Bacteria isolated	Clinical diagnosis
Adenovirus type 1	20	—	+	+	+	0	—	—	—	—	Otitis media
Adenovirus type 1	27	+	—	+	—	0	—	Adenovirus	—	Urine <i>E. coli</i>	Otitis media
Adenovirus type 1	56	—	—	+	+	—	+	—	—	—	Otitis media
Adenovirus type 1	59	+	+	—	+	—	—	—	NPS rhinovirus	CSF and blood <i>H. influenzae</i>	Meningitis
Adenovirus type 3		—	—	+	+	+	—	—			
Adenovirus type 2	7	—	+	—	+	0	+	Adenovirus persistent high titre	—	—	Otitis media
Adenovirus type 2	8	+	—	—	—	0	—	Adenovirus	—	—	URTI
Adenovirus type 2	13	—	—	+	+	0	+	—	—	—	Tonsillitis
Adenovirus type 2	44	—	—	+	+	0	—	Adenovirus	—	Throat. <i>Haemophilus</i>	Otitis media
Adenovirus type 2	67	—	+	—	+	+	(+EM)	Adenovirus	—	—	Tonsillitis
Echo type 3	63	—	+	—	+	—		—	—	Throat. <i>Streptococcus pneumoniae</i>	URTI
Echo type 3	71	—	+	+	+	0	0	—	—	—	PUO
Coxsackie A10	50	—	+	—	—	0	+	—	—	—	Pharyngitis
Coxsackie B2	61	—	+	+	+	+	0	—	—	Throat. <i>Haemophilus</i>	Pharyngitis
Coxsackie B3	46	—	+	+	+	+	+	—	—	Throat. <i>Haemophilus</i>	PUO
Parainfluenza type 2	9	—	+	—	+	0	—	Paraflu type 2	—	Throat. <i>Streptococcus G</i>	Croup
Parainfluenza type 3	72	+	—	+	—	+	0	—	—	—	Pharyngitis
Measles	38	—	—	+	+	+	0	Measles	—	—	Measles
Measles	39	—	+	—	—	—	—	Measles	Stool polio type 3	—	Measles
Measles	70	—	+	+	+	+	—	Measles		—	Measles vaccine
Cytomegalovirus	6	—	—	+	—	0	—	—	—	—	Tonsillitis
Totals	20	4	12	13							

+ Virus isolated, — no virus isolated, 0 no specimen taken.

URTI = upper respiratory tract infection, PUO = pyrexia of unknown origin, NPS = nasopharyngeal secretions.

The mean rectal temperature recorded immediately after admission was 39.5°C and ranged from 37.5 to 42°C. 11 (15%) children had received at least one dose of an antibiotic before collection of specimens for microbiology.

The clinical diagnoses of the precipitating illnesses were classified according to the guidelines suggested by Court (1973). An upper respiratory tract infection (URTI) was further described as coryza, tonsillitis, pharyngitis, or otitis media if the predominant symptoms or signs were localised to the nose, tonsils, pharynx, or tympanic membranes respectively. In Tables 1, 2, and 3 the diagnoses are tabulated against the pathogens which were subsequently identified. A morbilliform or maculopapular rash was reported during the illness of 14 patients, and pathogens identified from these cases are listed in Table 4. No pathogens were found in 18

patients whose diagnoses were tonsillitis (1), pharyngitis (2), otitis media (3), coryza (1), URTI (7), gastroenteritis (2), gastroenteritis with URTI (1), and pyrexia of unknown origin (1).

Upper respiratory illnesses were found in 59 (81%) of all patients and gastrointestinal illnesses in 9 (12%). These figures are close to those recorded in other surveys (Millichap, 1968).

49 (67%) patients had had fits each one lasting under 15 minutes, which was not followed by further fits in the same illness, and was not accompanied by localising signs. These were classified as 'simple fits'. One or more 'complex' features occurred in the remaining 24 (33%) patients. Eight patients had fits which each lasted longer than 15 minutes (but only 2 convulsed for longer than 30 minutes). 10 patients had more than one convulsion in the same illness, and 5 patients had localising features or a

Table 3 Results of bacteriology with clinical diagnoses. (Number of patients in parentheses)

Site	Organism	Diagnosis
Throat (16)	Streptococcus group A (1)	Tonsillitis (1)
	Streptococcus group G (1)	Otitis media (1)
	<i>S. pneumoniae</i> (3)	Tonsillitis (1), URTI (1), influenza (1)
	Haemophilus species (10)	Tonsillitis (1), pharyngitis (1), otitis media (3), URTI (3), gastro- enteritis with orchitis (1)* PUO (1)
	Streptococcus G. with Haemophilus (1)	Otitis media (1)
Stool (2)	<i>Shigella sonnei</i> (1)	Dysentery (1)**
Blood with CSF (1)	<i>E. coli</i> O111 (1)	Otitis media† (1)
	<i>H. influenzae</i>	Meningitis‡
Urine (2)	<i>E. coli</i> (2)	SBE (1), otitis media § (1)

*Coxsackie B1 also isolated (throat and stool), **adenovirus 2 (stool) also isolated (see Table 1), †CMV (throat) and echo 5 (stool) also isolated, ‡Case 59 (see Table 2), §Case 27 (see Table 2).
SBE = Subacute bacterial endocarditis.

Table 4 Virological findings in 14 patients with rashes. (Number of patients in parentheses)

Echovirus type 3 (1)
Coxsackie A10 (1)
Adenovirus type 2 (2); type 3 (1)
Cytomegalovirus (1)
Measles (2)
Measles CFT with respiratory syncytial virus CFT (1)
Cytomegalovirus with echovirus type 5 (1)
Adenovirus type 1 with parainfluenza type 3 and Coxsackie A10 (1)
Parainfluenza type 3 with Coxsackie A10 (1)
Coxsackie A4 with measles CFT (1)
No virus (1)

subsequent hemiparesis, but none had signs which persisted for longer than 24 hours. Six patients stopped convulsing only after they had been given parenteral anticonvulsants in hospital.

Patients with 'complex' convulsions had a similar spectrum of viral and bacterial findings as those with 'simple' convulsions, and the same incidence of blood and urine viral isolations. Convulsions had 'complex' features in 2 of the 4 patients carrying a

Table 5a Comparison of findings in febrile convulsions and gastroenteritis: virology results

Type of virus	Throat swab isolations		Stool isolations—tissue culture		Stool electron microscopy	
	Febrile convulsions (71 patients)	Gastroenteritis (125 patients)	Febrile convulsions (62 patients)	Gastroenteritis (150 patients)	Febrile convulsions (62 patients)	Gastroenteritis (150 patients)
Adenovirus	12 (17)*	4 (3)*	12 (19)	17 (11)	2 (3)	3 (2)
Enterovirus	6 (9)	2 (2)	5 (8)	12 (8)	2 (3)	3 (2)
Parainfluenza	3 (4)	1 (1)				
Cytomegalovirus	4 (6)	5 (4)				
Influenza	1 (1)	0				
Measles	2 (3)	0				
Respiratory syncytial virus	0	1 (1)				
Rhinovirus	1 (1)	3 (2)				
Herpes simplex	0	1 (1)				
Rotavirus					2 (3)*	76 (51)*
Calici, corona, or astrovirus					0	4 (3)
Totals	29 (41)*	17 (14)*	17 (27)	29 (19)	6 (10)*	86 (57)*

* $P < 0.01$ by χ^2 test.

Percentages are given in parentheses.

Table 5b Comparison of findings in febrile convulsions and gastroenteritis: bacteriology results

Pathogenic bacteria	Throat swab isolations		Pathogenic bacteria	Stool isolations	
	Febrile convulsions (70 patients)	Gastroenteritis (135 patients)		Febrile convulsions (67 patients)	Gastroenteritis (150 patients)
Streptococcus group A	1 (1)	3 (2)	<i>E. coli</i> (enteropathic)	1 (1)	2 (1)
Other haemolytic streptococci	1 (1)	7 (5)	<i>Shigella</i>	1 (1)	8 (5)
<i>S. pneumoniae</i>	3 (4)	4 (3)	<i>Salmonella</i>	0	11 (7)
Haemophilus species	10 (14)	8 (6)	<i>Campylobacter</i>	0	5 (3)
Streptococcus group G with Haemophilus	1 (1)				
Totals	16 (23)	22 (16)		2 (3)*	26 (17)*

* $P < 0.01$ by χ^2 test.

Percentages are given in parentheses.

virus in the CSF but one of these (Case 59) had *H. influenzae* meningitis (Table 2).

No relationship was found between 'complex' features and the WBC of the CSF or blood or the temperatures recorded after admission.

Microbiological findings in gastroenteritis

A concurrent but separate study of gastroenteritis comprised 150 children whose ages were similar to those with febrile convulsions (Lewis *et al.*, 1979). Both projects were undertaken by the same people and microbiological methods were identical. Viral and bacterial cultures were taken from stools and throat swabs, and stools were examined for rotavirus by electron microscopy. CSF, blood, and urine were not collected, nor were mouse inoculation tests performed.

The two groups of patients are compared in Table 5. Significantly more patients with febrile convulsions carried viruses in their throats. In gastroenteritis, rotavirus was by far the most common pathogen and bacterial pathogens were more often identified in the stool.

Discussion

The results indicate that common viruses can invade the blood stream and CSF and, presumably, the central nervous system. We suggest that systemic invasion occurred in all cases and was important in producing both fever and convulsion. We failed to isolate a virus from all specimens of blood and CSF because we took very small (1 ml) quantities, and we suspect that the virus was rapidly eliminated from these sites as the child recovered from the convulsion.

The study has shown a viral aetiology in a higher proportion of patients than others have reported (Wallace and Zealley, 1970; Familusi *et al.*, 1972; Stokes *et al.*, 1977), probably because several methods of viral diagnosis were used. Tissue culture from fresh specimens gave the highest number of positive results, and additional viruses were detected by electron microscopical examination and inoculation of suckling mice. Complement fixation tests were rarely positive, but we did not seek an immune response further by titrating neutralising antibody against the specific viruses cultured. Interferon assay was an indication of viral illness rather than definitive diagnosis. We detected interferon in the serum of 16 (36%) out of 45 patients from whom a virus was identified by tissue culture or serology, but we also found interferon in 15 patients from whom no virus was isolated. A previous study from this unit detected interferon in the acute phase serum of 17 (38%) out of 45 children and adults with

a proved virus infection, but from none of 25 with bacterial, mycoplasma, or rickettsial infections, or from 61 healthy persons (Matthews and Lawrence, 1979). We suggest that a virus was present but not demonstrated in our 15 patients with interferon but no other evidence of viral infection. This is not an unreasonable assumption as we did not perform tests for a number of viruses, including EB virus and hepatitis viruses.

We cannot prove that the viruses we identified were responsible for the illnesses which precipitated the convulsions, but we have good supportive evidence.

Firstly, a virus of the same type was often isolated from multiple sites in the same patient, and there was no cross contamination. The complement fixation tests often (but not always) corroborated the findings.

Secondly, the clinical features associated with the viruses agree well with those described in reports (Tables 1, 2, and 3). Thus, the adenoviruses and the parainfluenza viruses were particularly associated with tonsillitis and otitis media (Medical Research Council, 1965; Gardner, 1968; Clarke, 1973; Pereira, 1973). Diarrhoea was associated with rotavirus and with adenoviruses (Du Pont *et al.*, 1977; Walker-Smith, 1978). Rashes were observed with measles virus and Coxsackie A viruses (Table 4). Coxsackie B1 was identified in the stool and throat swab of a patient who had gastroenteritis followed by orchitis, and an enterovirus was found in 3 out of 4 children for whom pyrexia of unknown origin was the only diagnosis (Dalldorf and Melnick, 1965; Melnick, 1965; McLean, 1966). Four patients were immunised in the 2 weeks before their convulsions, but in 2 (DTP and polio vaccines) viruses were isolated which were possibly of more significance than the vaccine in precipitating the convulsion; in the third case cholera vaccine was given 1½ hours before the temperature suddenly rose with a convulsion and an unusually severe local inflammatory response. In the fourth case measles virus was isolated from the blood of a child who had measles vaccine 10 days before the convulsion. We have seen no other documented case of measles viraemia attributed to the febrile reaction to immunisation (Landrigan and Witte, 1973).

The different pattern of viruses identified in children with gastroenteritis adds further support to the validity of our findings (Table 5). Rotavirus has always been associated with diarrhoea, but adenoviruses and enteroviruses could be responsible for either respiratory or gastrointestinal illness, depending on their site of maximal multiplication (Dalldorf and Melnick, 1965; Ginsberg and Dingle, 1965; Melnick, 1965; Pereira, 1973; Steinhoff, 1978). Of doubtful significance were bacterial

pathogens in throat swabs, which were isolated with similar frequency in gastroenteritis and febrile convulsions, and have been commonly found in the throats of healthy young children (Masters *et al.*, 1958; Gardner, 1968). Although many children with febrile convulsions had clinical tonsillitis, a haemolytic streptococcus group A was isolated from only one throat.

We have implicated a systemic viral illness in the majority of febrile convulsions, but a generalised bacterial illness was possible in 3 (4%) cases where a bacterial pathogen was isolated from the CSF, blood, or urine (Table 3). The first child (Case 59) had clinical meningitis attributed to *H. influenzae*; we cannot explain the significance of finding two types of adenovirus in the CSF, blood, throat, and urine of this patient (Table 2). The second child had *E. coli* bacteriuria, but *E. coli* in a subsequent blood culture confirmed a diagnosis of bacterial endocarditis. The third patient (Table 2, Case 27) had significant but asymptomatic bacteriuria with clinical otitis media; an adenovirus was isolated from the CSF and urine, and there was a rising CFT titre to adenovirus.

We investigated only those with convulsions but transient viraemia or bacteraemia may occur in other children during acute febrile illnesses. We suggest that a convulsion occurs when a child with a predisposition to febrile convulsions is exposed to a systemic virus or bacterium at an age when the immature brain is susceptible (Coyle, 1976; Ounsted, 1976b). We had evidence of no predisposing factors except family history. After one year the occurrence of subsequent febrile convulsions in our cohort bears no relationship to the nature or site of the pathogen in the initial episode.

It has recently been shown (Stephenson, 1978) that not all febrile convulsions are classical epileptic paroxysms but some may be related to vagal reflexes. We may therefore have studied the microbiology of a heterogeneous group of central nervous system phenomena described as 'febrile convulsions'. We hope that more thorough virological investigations will be undertaken in conjunction with electrophysiology, immunology, and epidemiology to show how viruses can affect the central nervous system in different ways, ranging from a brief convulsion to a florid encephalitis or to a slow virus illness such as subacute sclerosing panencephalitis.

We thank the technicians in the Department of Microbiology, Mrs A. Mott and Dr E. C. Coles for statistical advice, Mrs R. C. White for typing the manuscript, Dr M. Liberman for allowing us to study patients, and the nursing staff and house physicians of Carroll Ward for assistance.

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Received 16 January 1979