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Viral infection as a precipitant of wheeze in children

Combined home and hospital study

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SUMMARY Sixteen children with asthma were studied for one year and viral isolation attempted during all episodes of wheezing. In 91 episodes investigated, 13 viruses were isolated (isolation rate 14%), whereas only one virus was isolated from 120 specimens taken when the children were symptom free. Rhinovirus was the commonest isolate and most were obtained during August, September, and October. Episodes of wheezing associated with virus infection were not clinically different nor more severe than those due to other precipitants.

Upper respiratory tract infection is one of the apparent precipitants of wheezing attacks in children. A relationship between viral infection of the upper respiratory tract and wheeziness has been shown in several studies—hospital inpatients (McIntosh *et al.*, 1973), hospital outpatients (Minor *et al.*, 1974a, 1976), and general practice (Horn *et al.*, 1975). Some have been confined to the winter months and case selection has been biased by the exclusion of children whose wheezing attacks were thought not to be precipitated by infection (Berkovich *et al.*, 1970; McIntosh *et al.*, 1973; Minor *et al.*, 1974a, 1976). We recently reported a 3-year hospital based study (Mitchell *et al.*, 1976) free from these constraints of timing and case selection and confirmed the association of viral infection and wheeziness. The selection of appropriate controls presents difficulties and to overcome this viral culture has been attempted in index patients during wheeze-free periods (McIntosh *et al.*, 1973; Minor *et al.*, 1976).

This study was undertaken to determine the incidence, nature, and seasonal variation of viral infection in children with recurrent wheeziness. The children were chosen consecutively, whatever the suspected precipitant of wheeze, and were studied for one year. Viral culture was attempted during all exacerbations of wheeze, whether or not viral infection was suspected on clinical grounds or admission to hospital occurred. The clinical features of wheezy episodes were noted. By attempting viral culture during symptom-free periods control data were obtained.

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Patients and methods

Sixteen children attending the respiratory clinic at the Royal Hospital for Sick Children were enrolled in the study between 1 January and 31 March 1975 and remained in the study for one year. They were selected if they had had three or more wheezing attacks during the preceding year, if they lived within Edinburgh, and had a telephone at home. The permission of parents and general practitioners was obtained. Table 1 gives clinical details. There were 7 boys and 9 girls whose mean age at the start of the study was 4·5 years (range 2·1–6·3). The age of onset of respiratory symptoms varied from 3 months to 5 years. 10 children had previous hospital admissions, 7 gave a history of eczema, 3 hay fever, and 2 were allergic to eggs. All were within normal limits for height and weight and had a normal chest *x*-ray and peak expiratory flow rate between attacks. 13 gave positive skin tests to a variety of allergens, 7 had an eosinophil count in peripheral blood of $>1{\cdot}0\times10^9$/l and 4 had a raised IgE concentration in blood. They received regular treatment throughout the study. There was a history of asthma, eczema, hay fever, or urticaria in the first-degree relatives of 14 patients.

Diaries were issued every 6 weeks (Fig. 1) to facilitate analysis of the prodromata and clinical features of the attacks. New episodes of respiratory illness were reported and patients seen at home within 48 hours by one of us (I.M.). Apparent precipitants were noted and clinical signs of upper or lower respiratory tract infection sought. Nasal and throat swabs were taken for viral cultures. Acute episodes were treated by the general practitioner. Patients were reassessed clinically every 6 weeks and swabs again taken for viral culture. These were

Table 1 *Clinical details*

Patient							*First-degree relatives*	
Case no.	*Sex*	*Age at start of study (yr)*	*Age at onset of respiratory symptoms (yr)*	*No. of hospital admissions before study*	*Eczema (past or present)*	*Regular treatment during study*	*Asthma*	*Eczema, hay fever, urticaria*
1	M	3·6	1·9	3	+	S	−	+
2	M	6·2	3·0	3	−	SCG	+	+
3	M	4·4	0·3	3	+	B	+	+
4	M	4·2	0·8	0	−	B	+	+
5	M	6·3	2·0	0	−	B	−	+
6	M	2·9	1·0	2	+	B	+	+
7	M	4·5	0·3	0	+	S	+	+
8	M	3·2	0·8	0	−	S	−	−
9	M	2·1	1·5	3	−	S	+	−
10	F	5·3	1·5	0	−	S	−	−
11	F	3·2	2·0	3	+	S	+	+
12	F	4·1	0·8	1	+	B	+	+
13	F	5·2	5·0	1	−	B	+	−
14	F	5·4	5·0	8	−	SCG	+	+
15	F	6·3	2·0	0	−	B	−	+
16	F	5·3	3·0	10	+	B	−	+

S = salbutamol (oral or inhaled); SCG = sodium cromoglycate; B = beclomethasone dipropionate aerosol.

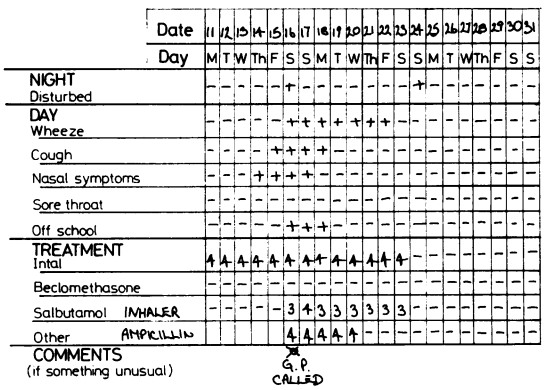

Fig. 1 *Diary card issued to patients. + or − indicates symptoms present or absent. The numbers refer to doses of medication.*

considered to be 'control specimens' if the children were symptom free and remained so for a further 5 days.

All swabs were placed immediately in Hanks's balanced salt solution + 0·2% bovine albumin, and 83% taken to the virus laboratory within one hour. 17% of the specimens taken during acute episodes and 11% of the control specimens were kept in a refrigerator at 4°C overnight before transfer to the laboratory. All specimens were inoculated on to cell cultures within 2 hours of arrival at the laboratory, being kept at 4°C throughout. On two occasions cell cultures were not available; the specimens were then stored at −70°C until cultures were available. The subsequent culture techniques have been described (Simpson *et al.*, 1974).

Results

Table 2 shows that there were 127 episodes of wheezing and virus culture was attempted in 91 (72%). Omissions were sometimes unavoidable, for example when the child was away from home or when the parent delayed more than a day or so in reporting to us. 13 viruses were isolated (isolation rate 14%). The number of viruses isolated from individual patients varied, but no more than 3 were isolated from any one patient. There were no viral isolates from 5 patients (one with 11 episodes investigated), and one patient was symptom free throughout the study. The commonest isolates were rhinovirus (5 occasions) and Coxsackie A9 (3 occasions). Only one virus, a polio virus type 1 in a child immunised a few days previously, was isolated from the 120 control specimens.

Fig. 2 shows the monthly distribution of episodes of wheezing and virus isolation. There was some variation in the number of episodes of wheezing per month, but this was not marked, being lowest in July and highest in September and October. More than half the isolates were obtained during August, September, and October, the other viruses being seen at varying times and no isolates in May, June, July, or December.

Fig. 3 shows the relationship between the initial diagnosis and the subsequent virological results. 56 episodes of wheeze were thought to be associated with upper respiratory tract infection and 7 isolates were obtained (13%); in 35 episodes, in which the precipitant was thought to be other than infection. there were 6 isolates (17%).

Preceding nasal symptoms were also unhelpful in

Table 2 *Results of virus culture*

Case no.	*No. of episodes of wheezing*	*No. with viral culture attempted*	*Viruses isolated*	*No. of control visits*	*Virus isolated*
1	9	7	Coxsackie A9	8	0
2	3	2	Rhinovirus	7	0
3	12	9	Echo 19; rhinovirus (2 isolates)	8	0
4	17	11	Rhinovirus; adenovirus 1	5	0
5	5	4	0	7	0
6	8	6	0	5	0
7	9	7	Coxsackie A9	5	Polio 1
8	8	2	0	8	0
9	9	8	Adenovirus 2	8	0
10	11	8	Rhinovirus	7	0
11	8	4	Respiratory syncytial virus	10	0
12	11	11	0	9	0
13	5	4	0	9	0
14	6	4	Parainfluenza 1	6	0
15	0	0	0	9	0
16	6	4	Coxsackie A9	10	0
Total	127	91	13	121	1

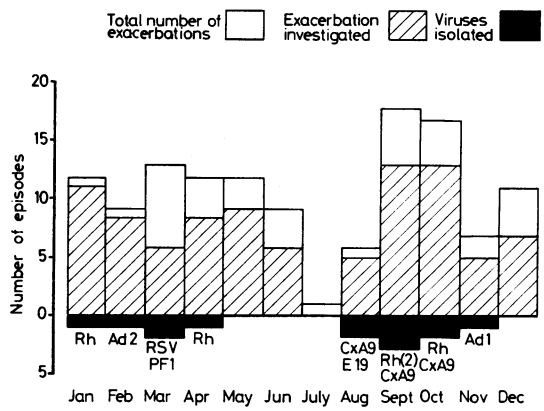

Fig. 2 *Monthly variations in exacerbations of wheezing and virus isolations. Rh = rhinovirus; Ad 1 & 2 = adenovirus types 1 & 2; RSV = respiratory syncytial virus; PF1 = parainfluenza type 1; CxA9 = Coxsackie type A9; E19 = Echo type 19.*

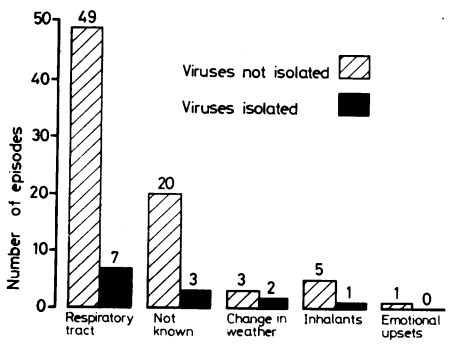

Fig. 3 *Apparent precipitant and subsequent virological results.*

the diagnosis of viral infection, being present in 5 of the 13 episodes with positive virology (38%) and in 23 of the 78 virus-negative episodes (13%). The 12 admissions were of 5 patients (Cases 1, 3, 6, 9, 11) of whom one (Case 9) was admitted 6 times. The duration of wheeze (mean ± SD) in the 13 episodes precipitated by viruses was 4·1 ± 2·6 days and in the 78 other episodes 4·8 ± 2·9 days. We have no evidence that proven viral infection increases the severity (by these criteria) of wheezing episodes.

All specimens were taken within 5 days of the onset of symptoms. 60 episodes were investigated within 48 hours and in 10 (17%) virus culture was positive. 31 specimens were taken 3, 4, or 5 days after onset and 3 were positive (10%). From the 17 specimens taken during acute wheezy episodes and stored overnight, 4 viruses were isolated. An additional 11 episodes of respiratory illness ('colds') not associated with wheeze were investigated but not included in the analysis. Two viruses (parainfluenza 3 and influenza A) were isolated.

Discussion

Our virus isolation rate (14%) is similar to that in a 3-year study of children with acute asthma investigated on admission to hospital (Mitchell *et al.*, 1976). However, many of the previous studies (Table 3) relating viral infection and wheeziness in children are not directly comparable. Neither of the studies of Minor *et al.* (1974a, 1976) continued throughout one complete year, and viral isolation was only attempted when respiratory tract infection appeared to be the precipitant of the acute attack of asthma. Thus difference in design and more frequent sampling during episodes of wheeze may explain the higher

Table 3 *Review of published reports of virus infection and wheezing in children*

Base	*Study*	*Index cases*	*Age (yr)*	*Duration (yr)*	*No. of patients*	*Episodes of wheezing*	*No. of virus identifications** (%)	*Main virus n (%)*	*Controls*	*Comment*
Hospital										
Acute admission	Disney *et al.* (1971)	'Acute asthma'	'Children'	1	51	51	3 (6)	—	'Respiratory infection without wheeze'— 11 isolates from 47 admissions (23%)	Specimens taken on admission to hospital—no risk of cross-infection
	Mitchell *et al.* (1976)	'Acute wheezy attacks'	1–12	3	192	360	39 (14)	Rhinovirus 16 (41)	—	As above; specimens taken whatever the apparent precipitant of wheeze
Inpatients (long-term)	McIntosh *et al.* (1973)	'Respiratory infection in severe asthma'	1–5	0·7 (Oct–May) & Oct–April on 2 consecutive years)	32	139	58 (42)	Respiratory syncytial virus 24 (41)	Index cases as monthly intervals —38 virus isolates when wheeze free	Potential risk of hospital cross-infection; controls not necessarily symptom free
Outpatients	Berkovich *et al.* (1970)	'Respiratory infection in asthma'	0·5–16	0·5 (Sept–Feb)	136	88	33 (38)	Influenza A2 12 (36)	—	Large default rate (38%)
Hospital & community										
Outpatients & domicilary	Minor *et al.* (1974)	'Respiratory infection in asthma'	3–11	0·7 (Oct-May)	16	61	24 (39)	Rhinovirus 15 (63)	Index cases twice weekly—23 virus isolates when wheeze free	Study of apparent respiratory infection in asthma; controls not necessarily symptom free
	Minor *et al.* (1976)	'Respiratory infection in asthma'	3–60 (8 aged over 17)	0·8 (Sept–June)	48	71	17† (24)	Rhinovirus 7 (41)	Index cases 2 weeks after acute episode—15 virus isolates when wheeze free	As above; children's data not analysed separately
	Present study	Asthma	2–6	1	16	91	13 (14)	Rhinovirus 5 (39)	Index cases at 6 weekly intervals —one virus isolated from 121 specimens	Specimens taken irrespective of apparent precipitant; controls completely symptom free
Community										
General practice	Horn *et al.* (1975)	'Respiratory infection ± wheeze'	0–12	5	—	554	152 (27)	Rhinovirus 68 (42)	—	Study of clinical features of viral respiratory infection

*Viruses identified by culture, apart from Berkovich *et al.* (1970) who identified 30 viruses by serology.
†14 isolates in patients aged 3–17.

isolation rate they obtained. However, as our results showed that apparent respiratory infection, wheezing, and viral isolation do not correlate well, other factors may be involved. In studies of different populations and design, wide variations in virus isolation rates are seen, ranging from 6% obtained by Disney *et al.* (1971), in acute admissions to hospital, to 42% by McIntosh *et al.* (1973) in long-term hospital inpatients. In a 5-year general practice survey, Horn *et al.* (1975) found a virus isolation rate of 27·7% in children who wheezed with apparent respiratory infections.

Difficulty in selecting controls has been common to most studies. Disney *et al.* (1971) used as controls 47 children admitted with respiratory infection without wheeze and found a virus isolation rate of 23% compared with 4% in asthmatic children admitted during the same period. Nonasthmatic sibs have also been used (Minor *et al.*, 1974b) but cannot be matched for age, sex, or school environment. McIntosh *et al.* (1973) and Minor *et al.* (1974a, 1976) used index cases as their own controls and isolated viruses (parainfluenzae types 1, 2, and influenza A2) in control specimens. The isolation rate in completely symptom-free children is not clear. Their conclusion that virus isolation is less likely in symptom free children accords with ours and suggests that the viruses isolated during wheezing episodes are indeed the precipitants.

Rhinoviruses are the commonest viral precipitants of wheeze, forming some 40% of the isolates in most studies (see Table 3). The primacy of respiratory syncytial virus in one study (McIntosh *et al.*, 1973) may be due to timing—during the winter months, the age of the patients, and possible exposure to hospital cross-infection. Respiratory syncytial virus has been identified less often in wheezy children in other studies, though it is the commonest pathogen in acute bronchiolitis of infancy. There is no clear evidence that other viruses are as consistently associated with wheeziness, although some, e.g. parainfluenza and influenza A, have been isolated from wheezy children by most of the above workers.

The question arises whether our low isolation rate of viruses resulted from inadequate techniques. Our methods of collecting and transporting specimens and the laboratory techniques compare with those of other investigators. Specimens were taken immediately to the laboratory and no child was investigated more than 5 days after the onset of symptoms. Horn *et al.* (1975), studying the effect of storage of specimens at 4°C overnight, showed that this did not affect the viral isolation rate. However, a slightly higher isolation rate might have been obtained by more frequent sampling during episodes of wheeze. It is likely that the viral isolation rate reflects the incidence of viral infection in these children and was not spuriously depressed to a significant extent.

We suggested previously (Mitchell *et al.*, 1976) that viral precipitants influence the severity of asthmatic attacks. However, we were unable to confirm this or to show that asthmatic children are particularly susceptible to viral infections as suggested by Minor *et al.* (1974b), both points being relevant to any consideration of the use of specific antiviral measures in asthmatic children. Our patients were representative of asthmatic children seen at a hospital outpatient clinic, the majority having a family history of asthma or atopic disorders, positive skin tests, and high IgE concentrations in peripheral blood. Several in whom we isolated viruses during wheezy episodes also gave a history of wheezing with other precipitants, such as exercise or exposure to pollens or dust. We would expect specific measures such as vaccination (McIntosh *et al.*, 1974) to be disappointing in such patients, even if this therapy were available. It is unlikely that vaccines to combat rhinovirus infection—the commonest viral pathogen—will be developed in view of the large number of rhinovirus serotypes. At present the mainstays of long-term treatment for many of these children will continue to be simple environmental control measures and the use of prophylactic drugs such as sodium cromoglycate or steroid aerosols.

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