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## Greater frequency of viral respiratory infections in asthmatic children as compared with their nonasthmatic siblings

*A longitudinal clinical and microbiologic surveillance was conducted from October to May, 1971-1972, on 16 children with infectious asthma and 15 of their nonasthmatic siblings. Asthmatic children experienced a significantly greater frequency of viral respiratory infections than did nonasthmatic ones (5.1 vs. 3.8 per subject). This increased incidence appeared to be largely the result of a greater number of rhinovirus infections. While respiratory infections of identical etiology that occurred concurrently in an asthmatic and his sibling were equivalent in severity, illnesses were longer (but not significantly so) in asthmatic children.*

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AN ASSOCIATION between episodes of symptomatic respiratory infection (SRI) and wheezing in children with intermittent reversible obstructive airway disease (asthma) has been clearly demonstrated.<sup>1,2</sup> Viral SRI plays a substantially greater role in the etiology of "infectious asthma" than does SRI of bacterial origin.<sup>1,4</sup> Attacks of asthma are less likely to be precipitated when symptoms of viral SRI are confined to a limited area of the respiratory system, e.g., the nasal or pharyngeal cavities, whereas wheezing is often provoked by more extensive SRI.<sup>2</sup> The exacerbation of asthma has been particularly associated with severe SRI caused by respiratory syncytial virus<sup>1</sup> and rhinoviruses.<sup>2</sup>

Because episodes of severe SRI frequently precipitate attacks of asthma in some children, the following questions are appropriate with regard to a comparison of these subjects with a nonasthmatic population: (1) are

they infected by the same types of respiratory pathogens, (2) are they more susceptible to respiratory infections and, therefore, ill more frequently, and (3) do they experience episodes of SRI which are more severe and/or of longer duration? Physicians and parents of asthmatic children have long suspected that asthmatics are more prone to respiratory infections. However, these questions cannot be answered on the basis of information available in the literature because, to our

Abbreviation used SRI: symptomatic respiratory infection
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knowledge, a longitudinal study of asthmatic children has not been conducted with an adequately controlled population of nonasthmatic children. Such a study should be performed on two populations which are exposed to the same respiratory pathogens.

This situation probably is most closely approximated by subjects who live together.<sup>5</sup> Accordingly, we conducted a clinical and microbiologic surveillance of 16 children with histories of infectious asthma and 15 of their nonasthmatic siblings. This study is part of a continuing investigation of the etiology and epidemiology of

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respiratory diseases<sup>2,5-8</sup> and of the pathogenesis of atopic and nonatopic asthma.<sup>9-12</sup>

## MATERIALS AND METHODS

Thirteen boys and three girls, ages 3-11 yr (average, 6.6), with histories of four or more attacks of asthma associated with respiratory illness during the previous year, were selected from nonhospitalized private patients of two of the authors (J. J. O. and M. C.). These children had no histories of asthma precipitated by food allergy, house dust, or pets but some of them were susceptible to asthma induced by pollens and molds during the summer. The control group was composed of nine of their brothers and six sisters, ages 4-9 yr (average, 5.7), with no histories of asthma or pulmonary signs of wheezing. Each asthmatic child had a normal sibling who was included in the study. Two of the asthmatics were brothers and only one control was included for them. Surveillance data and samples for microbiologic analysis were collected between Oct. 26, 1971, and May 25, 1972.

The health of each child was surveyed daily by the mother, two to three times weekly by a visiting registered nurse, and periodically by a physician. Respiratory infections were classified as asymptomatic, mild (signs or symptoms confined to a limited area of the respiratory system, i.e., cough, rhinitis/rhinorrhea, or pharyngitis/sore throat), or severe (involved more than one area of the respiratory system, e.g., cough and rhinorrhea, or mild infection accompanied by fever).<sup>\*</sup> An episode of infection was defined as >1 day in duration and separated from adjacent episodes by >4 days.<sup>2</sup> Any evidence of shedding of viruses was interpreted as an infection. Supposition for establishing the presence of bacterial infection was based on finding a potential pathogen which was not part of the individual's normal flora. These episodes invariably consisted of the shedding of large numbers ( $\geq 50$  at peak of shedding) of pathogens.<sup>2</sup>

Pharyngeal and nasal specimens (cotton swabs) were routinely obtained twice weekly for isolation of viruses, weekly for *Mycoplasma* and monthly for analysis of the bacterial flora. During respiratory illnesses, throat and nasal specimens for bacterial and viral analyses were generally obtained on three consecutive days soon after the onset of symptoms.

Blood samples were obtained quarterly for serologic analyses. Serology (neutralization titers) was employed

to test for concurrent rhinovirus and myxovirus infections in those instances where an isolate was obtained for one member of a sibling pair and not for the other. Because of the frequency with which A<sub>2</sub> influenza (Hong Kong) and rhinovirus type 49 were isolated, neutralization titers for these viruses were determined for all sera.

Methods of surveillance and microbiologic sampling were described in greater detail in a previous paper.<sup>2</sup> Methods used for the isolation and identification of infectious agents also were previously detailed.<sup>5,8</sup>

The data in Tables I and II were analyzed by Student's *t* test, with paired data. The data in Table III were analyzed by testing whether the difference between two proportions is null.

## RESULTS

The 16 asthmatic subjects experienced a total of 54 known episodes of viral infections, a significantly ( $P < 0.01$ ) greater incidence than the 35 similar episodes which occurred in 15 of their nonasthmatic siblings (Table I). Similarly, the incidence of respiratory infections of both viral and unknown etiology (the latter are most probably of viral origin) in asthmatics is significantly greater (81 vs. 57,  $P < 0.02$ ) than those which occurred in nonasthmatics. The incidence of respiratory infections of both confirmed and probable viral etiology per subject was 5.1 for asthmatics and 3.8 for nonasthmatics.

The increased incidence of viral infections observed in asthmatics appears to be accounted for, in large part, by an increased incidence of rhinovirus infections (Table I). However, the increased incidence of total (symptomatic plus asymptomatic) rhinovirus infections was not sufficient to be statistically significant. On the other hand, asthmatics did experience significantly (24 vs. 11,  $P < 0.01$ ) more symptomatic infections of rhinovirus etiology than did their siblings.

An analysis of total respiratory infections (which includes those of viral, bacterial, *Mycoplasma*, and unknown etiology) reveals that asthmatics, with 90 episodes (5.6 per subject), were not subject to a significantly ( $P > 0.15$ ) greater incidence than were their siblings with 73 episodes (4.9 per subject) (Table II). Contrary to the occurrence of viral infections, the incidence of bacterial respiratory infections was lower in asthmatics than in their siblings and this diminution accounts for the reduced excess of total infections in asthmatics. Of the episodes of SRI observed in asthmatics and their siblings, 63.5 and 58.5%, respectively, were associated with a known etiology.

To determine whether asthmatics were more easily infected by respiratory viruses than were their nonasthmatic siblings, an analysis was made of type-specific

<sup>\*</sup>The term "respiratory infection" is used by the authors to refer to SRI with known etiology, apparent infections (SRI with unknown etiology), and asymptomatic viral and bacterial infections. Apparent SRI with unknown etiology was assumed to be primarily viral in origin.

**Table I.** Incidence and etiology of viral respiratory infections in 16 asthmatic children and in 15 of their nonasthmatic siblings, October-May, 1971-1972

Etiology of viral respiratory infections	No. of episodes of viral respiratory infection in					
	Asthmatics			Nonasthmatics		
	SRI	Asymptomatic	Total	SRI	Asymptomatic	Total
<i>Myxoviruses:</i>						
Influenza A <sub>2</sub> (Hong Kong)	5	0	5	4	0	4
With group A streptococcus	2	0	2	1	0	1
With group C streptococcus	1	0	1	0	0	0
With <i>Streptococcus pneumoniae</i>	1	0	1	0	0	0
Parainfluenza types 1 and 2	2	1	3	2	1	3
Influenza B	1	0	1	0	0	0
<i>Picornaviruses:</i>						
Rhinovirus type 5, 9, 13, 20, 28, 29, 32, 48, 49, 58, 65, 78, 80, 81, untypable	24	6	30*	8	10	18
With group A streptococcus	0	0	0	3	0	3
Enterovirus-like agent	0	1	1	1	0	1
Respiratory syncytial virus	0	0	0	1	0	1
Adenovirus types 1, 2, 4, 5	2	2	4	1	1	2
Herpes simplex	2	3	5	0	2	2
With group A streptococcus	1	0	1	0	0	0
Total viral infections	41	13	54†	21	14	35
Apparent infections of unknown etiology (probably viral)	27	—	27	22	—	22
Total detectable infections of probable viral etiology	68	13	81‡	43	14	57
Incidence of total infections of probable viral etiology per subject	4.3	0.8	5.1	2.9	0.9	3.8

\*Total rhinovirus infections are not significantly ( $t = 1.644$ ,  $df = 15$ ,  $P > 0.05$ ) greater than those in nonasthmatics. However, episodes of SRI associated with rhinoviruses in asthmatics are significantly ( $t = 2.709$ ,  $df = 15$ ,  $P < 0.01$ ) greater than those in nonasthmatics.

†Known viral infections in asthmatics are significantly ( $t = 2.695$ ,  $df = 15$ ,  $P < 0.01$ ) greater than those in nonasthmatics.

‡Total infections of probable viral etiology in asthmatics are significantly ( $t = 2.366$ ,  $df = 15$ ,  $P < 0.02$ ) greater than those in nonasthmatics.

myxovirus and rhinovirus infections which occurred in members of the same sibling pair. Susceptibility to these viruses was estimated by noting the absence ( $<1:6$ ) of pre-existing neutralizing antibody. Asthmatics were infected by 85.7% of those agents to which they were susceptible and which infected their siblings (Table III). The rate of infection by these agents was significantly ( $P = 0.024$ ) lower in the nonasthmatics (56.3%). The increased number of infections observed in asthmatics was accounted for chiefly by the rhinoviruses (84.6 vs. 50.0%,  $P = 0.042$ ).

Twenty-four respiratory infections occurred concurrently in an asthmatic and his sibling which were of identical etiology (Table IV). These included 4 influenza A<sub>2</sub>, 3 parainfluenza, 12 rhinovirus, 1 herpes simplex, and 4 group A streptococcal infections. Agents which occurred concurrently were responsible for 13 severe, 4

mild, and 7 asymptomatic respiratory infections in asthmatics and for 14 severe, 2 mild, and 8 asymptomatic respiratory infections in nonasthmatics. The average duration of concurrent infections which resulted in mild or severe SRI was 6.1 days for asthmatics and 4.4 days for nonasthmatics (data not shown in tables). Although illnesses were of longer duration in asthmatics, this difference was not statistically ( $P > 0.05$ ) significant.

## DISCUSSION

The data presented in this paper indicate that (1) asthmatic children experienced a significantly greater incidence of viral respiratory infections than did their nonasthmatic siblings of similar age; (2) although both asthmatics and their siblings usually were infected by the same group or even serologic type of

**Table II.** Incidence and etiology of bacterial respiratory infections and their relation to other respiratory infections in 16 asthmatic children and in 15 of their nonasthmatic siblings, October-May, 1971-1972

Etiology of respiratory infections	No. of episodes of respiratory infection in					
	Asthmatics			Nonasthmatics		
	SRI	Asymptomatic	Total	SRI	Asymptomatic	Total
Bacterial infections*						
Group A streptococci M-types						
1, 2, 3, 6, 12, 43, untypable	4	2	6	9	5	14
<i>Streptococcus pneumoniae</i>	1	0	1	1	0	1
<i>Haemophilus influenzae</i>	1	0	1	0	1	1
Mycoplasma sp. (not <i>M. pneumoniae</i> )	0	1	1	0	0	0
Total bacterial and Mycoplasma infections	6	3	9	10	6	16
Total viral infections (from Table I)	41	13	54	21	14	35
Total viral, bacterial, and Mycoplasma infections	47†	16	63	31†	20	51
Apparent infections of unknown etiology (probably viral) (from Table I)	27	—	27	22	—	22
Total detectable respiratory infections	74	16	90‡	53	20	73
Incidence of total respiratory infections per subject	4.6	1.0	5.6	3.5	1.3	4.9

\*No viruses detected. Total bacterial infections (including those occurring with viruses) were 13 for asthmatics and 20 for nonasthmatics.

†Per cent of SRI with a known etiology was 63.5 for asthmatics and 58.5 for nonasthmatics. Seven of the 47 SRI in asthmatics and two of the 31 SRI in nonasthmatics were diagnosed on the basis of serology alone.

‡Total respiratory infections in asthmatics are not significantly ( $t = 0.933$ ,  $df = \text{mastic } 15$ ,  $P > 0.15$ ) greater than in nonasthmatics.

respiratory pathogen, the former had a significantly greater rate of infection by rhinoviruses; and (3) while respiratory infections of identical etiology occurring concurrently in an asthmatic and his sibling were equivalent in severity, illnesses were longer (but not significantly so) in the asthmatic children.

One might argue that the greater incidence of diagnosed viral respiratory infections observed in asthmatics is merely a laboratory artifact. However, those viral infections whose diagnoses were missed are most probably represented by episodes of SRI listed as etiology unknown. When the latter were included in the analysis with known viral infections, our original observation retained its validity.

The incidence of bacterial infections was lower in asthmatics than in nonasthmatics. However, our records reveal that asthmatics received more antibiotic therapy than did nonasthmatics. This treatment was probably responsible for the decreased incidence of bacterial infections in asthmatics and may have prevented us from observing a significantly greater incidence of total respiratory infections in this group.

Of interest are the high percentages (63.5 and 58.5) of episodes of SRI which were associated with a known etiology, particularly since no provision was made for the isolation of viruses such as the coronaviruses which are

difficult or impossible to detect in tissue cultures.<sup>13</sup> This compares favorably with a previously reported high isolation rate of 57%.<sup>14</sup> Our success in establishing etiology is largely attributable to (1) serial cultures and (2) the use of a sibling control. The latter enabled us to extend the probability of laboratory diagnosis by serologic techniques.

The finding that asthmatic children acquired more respiratory infections—especially rhinovirus infections—than their nonasthmatic siblings is presently inexplicable other than by speculation. It is probably unlikely that asthmatics are innately more susceptible than nonasthmatics to rhinoviruses, as inocula (nasal drops) containing as few as 0.4<sup>15</sup> or 0.032<sup>16</sup> 50% tissue culture infective doses have produced a rhinovirus infection in healthy adults. More likely, somehow, the asthmatic is placed in a circumstance whereby the virus is more easily transmitted to him than to a normal person. The rhinoviruses are actually quite difficult to transmit under natural conditions. We found no transmission of rhinovirus type 55 between groups of infected “donors” and serum antibody-free “recipients” when placed together for two or three hours in a small room, and only one of 14 “recipients” became infected when kissed by rhinovirus-55-infected “donors” for 1 to 1½ minutes.<sup>17</sup> Additionally, we have found a transmis-

**Table III.** Myxovirus and rhinovirus infections acquired by 13 asthmatic children and 13 of their nonasthmatic siblings, October-May, 1971-1972, in which members of the same family were concurrently exposed to the same type-specific agent\*

	Asthmatics					Nonasthmatics				
	No. of sibling's agents				Per cent infection†	No. of sibling's agents				Per cent infection†
	Exposed to	Immune to	Susceptible to	Infected by		Exposed to	Immune to	Susceptible to	Infected by	
Myxoviruses										
Influenza A <sub>2</sub> (Hong Kong)	5	0	5	4	80.0	7	1	6	4	66.7
Parainfluenza types 1 and 2	3	0	3	3	100.0	3	0	3	3	100.0
Influenza B	0	—	—	—	—	1	0	1	0	0
All myxoviruses	8	0	8	7	87.5‡	11	1	10	7	70.0
Rhinoviruses	17	4	13	11	84.6§	24	2	22	11	50.0
All agents	25	4	21	18	85.7	35	3	32	18	56.3

\*Data from two families omitted for lack of serum.

†Per cent infection = no. of sibling's agents infected by no. of sibling's agents susceptible to × 100.

‡Not significantly (P = 0.396) greater than that of nonasthmatics.

§Significantly (P = 0.042) greater than that of nonasthmatics.

|| Significantly (P = 0.024) greater than that of nonasthmatics.

**Table IV.** Severity of etiologically associated respiratory infections occurring concurrently in 16 asthmatic children and in 15 of their nonasthmatic (controls) siblings, October-May, 1971-1972

Agents	Severity of respiratory infections					
	Severe SRI*		Mild SRI†		Asymptomatic	
	Asthmatics	Controls	Asthmatics	Controls	Asthmatics	Controls
Myxoviruses						
Influenza A <sub>2</sub> (Hong Kong)	3	3	0	0	0	0
with group A streptococcus	1	1	0	0	0	0
Parainfluenza types 1 & 2	0	2	2	0	1	1
Rhinovirus types 5, 9, 32, 48, untypable	6	6	2	1	4	5
Herpes simplex	0	0	0	0	2	2
Group A streptococci M types 3, 6, 12, 43, untypable	3	2	0	1	0	0
Totals	13	14	4	2	7	8

\*Symptomatic respiratory infection with fever or &gt;1 sign or symptom present.

†Symptomatic respiratory infection consisting of 1 sign or symptom.

sion rate of only 40-50% between college-age, serum antibody-free married couples in which one member of the pair was artificially infected with either rhinovirus 16 or rhinovirus 55.\* This transmission rate among married couples is very similar to the 50% infection rate of the nonasthmatic children but markedly lower than the

84.6% rate of the asthmatics (Table III). It seems reasonable that this increased rate of infection for asthmatics may be related to their necessarily increased indoor life in a cold climate such as that found in Wisconsin. Such confinement could result in a longer exposure to the respiratory viruses shed by other family members.

It is noteworthy that those viruses which appeared to be responsible for a greater incidence of respiratory in-

\*D'Alessio, D. J., Peterson, J. A., and Dick, E. C.: Unpublished data.

fections in asthmatics, namely the rhinoviruses, were also the agents most likely to precipitate asthma in this group.<sup>2</sup> It would appear that the frequency of recurrent wheezing in children with nonatopic asthma is directly influenced by their families, i.e., the probability of wheezing may increase with the number of respiratory viruses which are introduced into the home. Until methods are made available to prevent transmission of respiratory viruses, the exposure of asthmatic children to individuals with respiratory infections should be minimized as much as possible.

The authors gratefully acknowledge the counsel of Dr. Warren H. Dennis, Department of Physiology, who reviewed the statistical analysis of data. Virologic and bacteriologic analyses were performed under the direction of Mrs. Judy Peterson and Mr. Douglas Docherty, respectively, with the assistance of Mrs. Jyy-Shiang Huang, WHO Fellow. Microbiologic sampling and clinical evaluations were conducted by Mrs. Ann Perry, R.N. Facilities and materials were furnished by the Wisconsin State Laboratory of Hygiene through the kindness of its director, Stanley L. Inhorn, M.D. Mycoplasma analyses and some grouping of streptococci were performed in the laboratories of Miss Virginia Allen and Miss Margaret Hutchinson, respectively (State Laboratory of Hygiene). Rhinovirus antisera were supplied by Dr. V. V. Hamparian of the Department of Pediatrics, Ohio State Medical School, Columbus, Ohio.

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