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## *The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children*

*The relationship between exacerbations of wheezing and infection of the respiratory tract was studied prospectively in 32 young hospitalized asthmatic children. Of 139 episodes of wheezing, 58 (42 per cent) were associated with identifiable viral infections. There were 25 respiratory syncytial virus infections; wheezing occurred in 24 of these and pneumonia in 13. Parainfluenza type 2 infection appeared to be next most likely to be associated with wheezing, followed by coronavirus infection. Influenza A (Hong Kong) was not associated with wheezing in any of the children. Infection with "pathogenic" bacteria was not statistically associated with wheezing.*

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THE RELATIONSHIP between infection of the respiratory tract and exacerbations of pulmonary symptoms in individuals with intermittent reversible obstructive airway disease (asthma) is well established on clinical grounds. However, despite many studies it has not been possible to implicate acute bacterial infection in exacerbations of wheezing in asthmatic individuals. Even more

uncertain is the role of bacterial allergy in the pathogenesis of asthma.<sup>1-4</sup> Recent studies using modern tissue culture technology have demonstrated that the majority of acute upper respiratory tract diseases in adults and of both upper and lower tract diseases in children is due to viruses. However, viral infections have not been systematically studied in asthmatic individuals, and published data attempting to relate such infection to acute wheezing attacks in asthmatic subjects are limited.<sup>5</sup>

Because of this paucity of information we initiated a prospective study of viral respiratory infection in young children with asthma hospitalized at the National Jewish Hospital in Denver. The first two years' experience in this study form the basis for this report.

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**METHODS**

**Children under study.** The children were inpatients hospitalized in the Pediatric Allergy Division of the National Jewish Hospital and Research Center. They were admitted for intensive diagnostic study and treatment because of a history of severe episodes of recurrent reversible obstructive airway disease. Two groups were studied: one group of 12 children studied between October, 1967, and May, 1968, and one group of 20 children studied between October, 1968, and April, 1969. The ages of the children ranged from 1 to 5 years at the onset of each study period; no child was present during both years of the study. All subjects remained hospitalized throughout the period of investigation except for two children who were discharged during January and February, 1969 in the second year of the study.

The majority of the children were receiving conventional bronchodilator therapy on a regular basis. Seven of the 32 were treated with maintenance doses of corticosteroids during the study period. Prednisone was required at low doses in three children (2.5 to 5 mg. every other day), moderate doses in two children (10 to 15 mg. every other day), and high doses in two children (20 to 40 mg. every other day in one child and 8 to 15 mg. every day in the other). Of the 32 children in the study 29 were classified as "atopic" on the basis of family or personal history of allergic rhinitis, asthma, or eczema, blood eosinophilia, and positive wheal and flare skin tests to foods and inhalants. The age and sex of the 32 children are shown in Table I.

**Epidemiologic methods.** Clinical records were kept for each child by a member of the study team (T. G. L. during 1967 to 1968 and L. H. during 1968 to 1969). At the onset of each acute respiratory illness, whether or not associated with wheezing, the child was examined. His symptoms and signs were recorded, and his course and response to therapy were followed. The care of the children was under the direction of Fellows in Pediatric Allergy, who were supervised by one of us (E. F. E.). Chest radiographs were obtained as the Fellows thought clinically indi-

**Table I.** Age and sex of children under study during 1967 to 1968 and 1968 to 1969

Age (yr.)	No. children		
	M	F	Total
1	7	2	9
2	2	3	5
3	1	3	4
4	4	5	9
5	2	3	5
Total	16	16	32

cated and were interpreted by members of the radiology department.

Within one to two days of the onset of each separate respiratory illness the following specimens were obtained: nasopharyngeal and throat swabs for virus and bacterial culture, and a venous blood sample. During 1967 to 1968 separate nasopharyngeal and throat swabs were obtained for Mycoplasma recovery. The decision to obtain these specimens was made by the individual keeping clinical records and was usually based on the presence of wheezing, rhinorrhea, fever, otitis, or cough. In addition to these "acute" specimens, during 1967 to 1968 nasopharyngeal and throat swabs for bacterial cultures were obtained routinely each week. During the second year of the study, routine nasopharyngeal and throat swabs for virus culture and venous blood samples were also obtained at approximately monthly intervals. In both years, "convalescent" blood specimens were obtained two weeks after "acute" samples.

**Culture methods.** Nasopharyngeal and throat swabs for virus recovery were inoculated within one hour of collection onto monolayers of WI-38, Rhesus monkey kidney, and HEP-2 cells, which were incubated at 36° C. Viruses were recognized and identified by standard techniques.<sup>6</sup> No attempts were made to recover coronaviruses using organ culture techniques.<sup>7</sup>

Swabs for bacterial culture were inoculated on sheep blood and chocolate agar. Mycoplasma cultures were performed from throat and nasopharyngeal swabs on enriched PPLO agar.<sup>8</sup> Because only two Mycoplasma recoveries (one *M. pneumoniae* and one *M. hominis*) were made during the first year,

**Table II.** Association of virus infection with disease in 12 asthmatic children, October, 1967, to

Index virus	Infections with index virus alone							
	No. of infections*	Infection associated with						No symptoms
		Wheezing	Intra-venous therapy	X-ray changes†	Upper respiratory infection	Otitis	Fever	
Respiratory syncytial	6 (3)	6	1	2/3	1	1	5	0
Parainfluenza 1	0	—	—	—	—	—	—	—
Parainfluenza 2	9 (7)	6	2	3/5	7	1	5	0
Parainfluenza 3	3 (3)	3	0	1/1	2	1	2	0
Influenza A <sub>2</sub>	1	0	0	0	0	0	0	1
Influenza B	0	—	—	—	—	—	—	—
Adenovirus	3	1	0	1/1	2	0	2	1
Coronavirus 229E‡	2	2	0	0/1	2	0	0	0

\*Number in parenthesis indicates number of infections where index virus was recovered.

†Number of chest x-rays showing infiltrate and/or atelectasis per number of chest x-rays taken.

‡Ten patients only studied.

the procedure was not performed during the second year.

**Serologic methods.** Venous blood samples were centrifuged within 18 hours of collection and serum was stored at  $-20^{\circ}$  C. Hemagglutination inhibition was performed to measure antibody to parainfluenza, influenza A<sub>2</sub>/Hong Kong (during 1968 to 1969 only), and coronaviruses OC38 and OC43.<sup>9</sup> Serum inhibitors were removed with receptor-destroying enzyme. Complement fixation tests were performed to measure antibodies to influenza A and B, adenovirus, respiratory syncytial virus, and coronavirus strains 229E,<sup>10</sup> OC38, and OC43.<sup>7</sup>

Coronavirus antigens were included because of their demonstrated importance in adult<sup>11, 12</sup> and pediatric<sup>13</sup> upper respiratory illness. Strains OC38 and OC43 have been shown to be identical in cross-neutralization tests using animal sera,<sup>14</sup> but both strains were included in our battery of tests. Every serologic rise in titer to strain OC38 was reflected in a similar rise in titer to OC43. For this reason, in our analysis these virus strains are combined under the name "coronavirus OC38-43." All rises in titer measured by complement fixation were also measured by hemagglutination inhibition.

**Clinical definitions.** For the purpose of this analysis, certain categories of respiratory disease were recognized. Upper respiratory infection was defined as either rhinorrhea or

pharyngitis or both, without otitis. Loss of bony landmarks was the minimal criterion of otitis media, and otitis media accompanied by an upper respiratory infection was considered as otitis media alone. Since cough was a complaint associated with almost every respiratory illness, it was not included in this analysis. Fever was defined as oral or rectal temperature over  $38.0^{\circ}$  C. Chest radiographs were considered acutely abnormal if they showed pulmonary infiltrates or atelectasis representing a clear change from the most recent previous film.

The presence or absence of wheezing was determined by physical examination. Severity of airway obstruction is difficult to score clinically in children under 5 years of age, but changes in bronchodilator medication, particularly the institution of intravenous therapy, represent a reasonably objective measure of the severity of acute asthma. For this purpose a "medication score" has been devised by assigning bronchodilators relative values and summing these for each patient each day. Corticosteroid medications are not included in this score.

**Definition and dating of infection.** If a culture obtained during an acute illness yielded a virus, then infection with that virus was said to be associated with that illness, and the infection was dated on the day of virus recovery, even though the illness might have begun a day or two before or after.

May, 1968

Combined infections with index virus and other virus(es)								
No. of infections*	Infection associated with							
	Wheezing	Intra-venous therapy	X-ray changes†	Upper respiratory infection	Otitis	Fever	No symptoms	Other viruses
1 (1)	1	0	0	1	0	0	0	Corona
1	1	1	1/1	0	0	0	0	Parainfluenza 2
1	1	1	1/1	0	0	0	0	Parainfluenza 1
0	—	—	—	—	—	—	—	—
0	—	—	—	—	—	—	—	—
0	—	—	—	—	—	—	—	—
1	1	1	0/1	0	0	0	0	<i>M. pneumoniae</i>
1	1	0	0	1	0	0	0	Respiratory syncytial

Serologic confirmation of such infection was defined by a fourfold or greater rise in antibody to that virus between acute and convalescent sera.

All antibody rises were either confirmed by repetition of tests or clearly defined by multiple serial serum samples. The following rules applied for the dating of infections defined by serologic change alone, when no virus was isolated. If an illness occurred in the interval between two serum samples showing a significant antibody titer rise, the first of these sera was, with rare exceptions (six times over the course of the study), obtained at the onset of the illness. The infection was then associated with the illness and dated at the time of appearance of symptoms. If no illness occurred between two serum samples which defined a titer rise, then the infection was considered asymptomatic and dated either two weeks before the "convalescent" sample (six instances) or, if the interval between the "acute" and "convalescent" samples was less than two weeks (six instances), at the time of the "acute" sample. Serum samples which defined a titer rise were never spaced more widely than 35 days. The average interval between serum samples during the entire study was 14 days.

#### Combined infection with multiple viruses.

In spite of the close spacing of serum samples in this study, evidence for combined infection with more than one virus was fre-

quent. Such double infections were always defined by the development of antibody titer rises to more than one virus, or to a virus different from that recovered at the time of the "acute" sample, and never by the simultaneous recovery of more than one virus. When the two viruses involved in such a combined infection were serologically unrelated, it was clearly impossible to decide which virus was of primary and which of secondary importance, and the viruses have been given equal emphasis in Tables II and III. Because of demonstrated antigenic interrelations within the group, combined antibody rises to the parainfluenza viruses were, with one exception, eliminated by assigning each such infection to the virus type which was recovered in tissue culture.

## RESULTS

**Proportion of wheezing episodes associated with virus infection.** As shown in Table IV, the 32 children had 102 identified separate viral respiratory infections, or an average of 3.2 infections per child. Fifteen of these infections were due to more than one virus. During 1967 to 1968 there were 70 episodes of wheezing among the 12 children under study, of which 23 (33 per cent) were associated with proved respiratory infection. During 1968 to 1969, 35 (51 per cent) of 69 acute wheezing attacks were associated with viral infection. Every child had at least one

**Table III.** Association of virus infection with disease in 20 asthmatic children, October, 1968, t

Index virus	No. of infections*	Infection with index virus alone						
		Infection associated with						
		Wheezing	Intra-venous therapy	X-ray changes†	Upper respiratory infection	Otitis	Fever	No symptoms
Respiratory syncytial	14 (10)	13	2	8/11	3	5	8	1
Parainfluenza 1	6 (2)	1	0	1/4	2	0	3	2
Parainfluenza 2	6 (5)	2	0	0/2	1	0	2	3
Parainfluenza 3	3 (1)	0	0	0/1	0	2	1	0
Influenza A <sub>2</sub> / Hong Kong	7 (2)	0	0	0	3	2	5	2
Influenza B	3	1	1	1/1	0	0	1	1
Adenovirus	10 (6)	3	1	2/2	2	2	4	3
Coronavirus OC38-43	10	7	2	3/7	5	2	4	0

\*Number in parenthesis indicates number of infections where index virus was recovered.

†Number of chest x-rays showing infiltrate and/or atelectasis per number of chest x-rays taken.

**Table IV.** Association of respiratory viral infection with wheezing in 32 asthmatic children

	1967-68	1968-69	Total
Number of children studied	12	20	32
Total number of respiratory viral infections*	29	73	102
Total number of acute wheezing episodes	70	69	139
Number of wheezing episodes associated with respiratory viral infection (% of total)	23 (33%)	35 (51%)	58 (42%)

\*Defined by either virus isolation or rise in serum antibody titer or both. This includes 15 infections by more than one virus (see text).

episode of wheezing associated with viral infection. The use and dosage of maintenance corticosteroids were not correlated, either positively or negatively, with the severity or frequency of wheezing with infection.

At those times when respiratory viruses were prevalent the proportion of wheezing illness which might be ascribed to infection was considerably higher. For example, in the interval between December 1, 1968, and February 2, 1969, while parainfluenza virus types 1 and 2, respiratory syncytial virus, and coronavirus OC38-43 were present in the hospital, 29 of 34 (85 per cent) wheezing illnesses were associated with virus infection.

**Virus epidemiology.** During 1967 to 1968 (Fig. 1), there were two small respiratory virus outbreaks, one due to respiratory syn-

cytial virus during April and one due to parainfluenza virus type 2 during January and February. The next year (Fig. 2), several viruses were epidemic. During late December and January 18 children were infected with respiratory syncytial virus and 9 children, with parainfluenza virus type 1. Only two children had simultaneous infections with both viruses. Likewise, during November and December both parainfluenza virus type 2 and coronavirus OC38-43 were epidemic. In addition, influenza A<sub>2</sub>/Hong Kong infected eight children in late October before a vaccination program was undertaken.

It is evident from Figs. 1 and 2 that in both years of the study exacerbations of wheezing coincided in time with respiratory virus infection. Both respiratory syncytial

April, 1969

Combined infections with index virus and other virus(es)								
No. of infections*	Infection associated with							
	Wheezing	Intra-venous therapy	X-ray changes†	Upper respiratory infection	Otitis	Fever	No symptoms	Other viruses
4 (2)	4	2	3/4	1	0	2	0	Parainfluenza 2 Parainfluenza 1 (2) Corona
3	3	1	2/3	1	0	1	0	Respiratory syncytial (2) Adeno
6 (3)	3	0	0/4	2	0	3	2	Respiratory syncytial Corona (5)
1	0	0	1/1	1	0	1	0	Influenza A
3	0	0	2/2	2	0	2	1	Adeno (2) Parainfluenza 3
0	—	—	—	—	—	—	—	
3 (2)	1	0	1/2	1	0	1	1	Influenza A (2) Parainfluenza 1
6	3	1	1/4	2	0	2	2	Parainfluenza 2 (5) Respiratory syncytial

virus outbreaks were reflected in increases in acute wheezing or pulmonary infiltrates. Another clear outbreak of wheezing occurred in a 3 week period beginning in late November, 1968, and coincided with infection by parainfluenza virus type 2 and coronavirus OC38-43.

**Respiratory syncytial virus infection.** Respiratory syncytial virus had clearly the highest attack rate and was the most consistently pathogenic of the respiratory viruses in these children (Tables II and III). Of the 32 children in both years of the study, 25 (78 per cent) were infected. Of these 25 infections, 24 were associated with wheezing, 13 with acute pulmonary infiltrates or atelectasis (radiographs were obtained in 18), 6 with otitis media, and 15 with fever.

Wheezing varied from mild to severe. A significant increase (4 points on the "medication score") in bronchodilator medication was required in 17 children, and 5 of them had intravenous therapy.

Pulmonary radiographic changes were interpreted as bronchopneumonic infiltrates in most of the children. Atelectasis occurred in two children and was accompanied by bronchopneumonia in one of them. Infiltrates were unilateral in eight and bilateral

in four. The most commonly involved area was the right middle lobe.

**Parainfluenza virus type 2 infection.** In contrast to respiratory syncytial virus, the association of parainfluenza virus type 2 infection with wheezing in the young asthmatic host appeared to be quite variable. During the first year of the study, this organism was more prevalent than respiratory syncytial virus. Moreover, it was associated with the same number of wheezing attacks as respiratory syncytial virus, more pulmonary infiltrates (4), and a larger number of severe episodes requiring intravenous therapy (3). On the other hand, although it was a common infection during the second year, it was then associated with only five wheezing episodes and no pulmonary infiltrates. Five infections were coincident with coronavirus OC38-43 antibody rises, two of which were associated with wheezing. None of the children in this study had croup in association with parainfluenza 2 infection. However, several non-asthmatic children hospitalized on the same ward did develop croup with parainfluenza 2 infection during the outbreak in 1967.

**Influenza virus infection.** During 1967 to 1968, only a single (asymptomatic) influenza virus type A infection occurred, and there

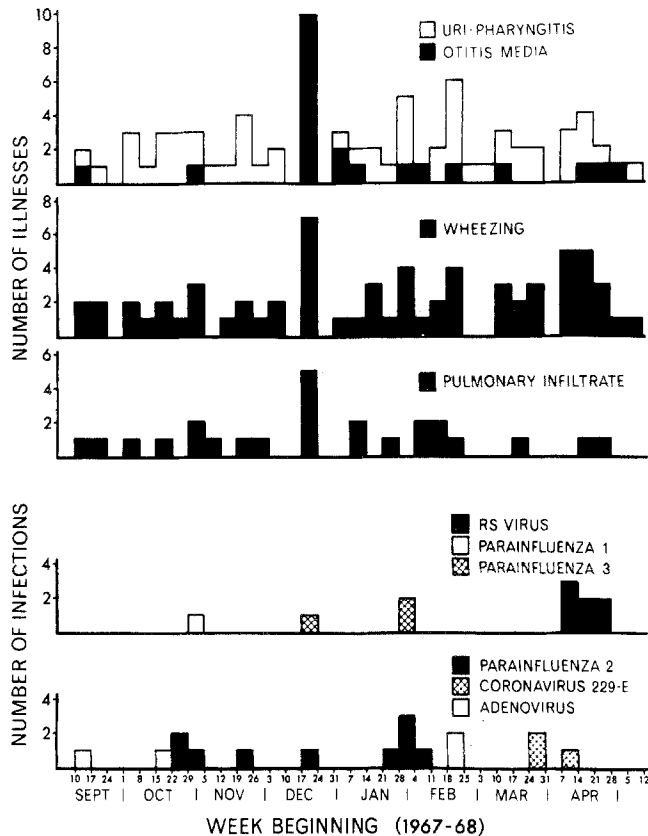


Fig. 1. Respiratory symptoms and illness in 12 asthmatic children in relation to respiratory viral infections (by weeks, 1967 to 1968).

were no influenza virus type B infections. The next year there were three type B infections, one of which was associated with a severe illness. During November, 1968, an influenza vaccination campaign was begun which included most of the study children. Nevertheless, 10 infections due to wild influenza A<sub>2</sub>/Hong Kong were identified, none of which was in previously vaccinated children. Of great interest was the complete lack of wheezing associated with influenza A<sub>2</sub>/Hong Kong infection, as was the mild nature of the illness. Three children were completely asymptomatic. Two children developed pneumonia which, in both cases, represented combined infections, one with parainfluenza 3 and one with adenovirus.

**Coronavirus infection.** Coronavirus 229E infected three children during 1967 to 1968, one of them in combination with respiratory syncytial virus (Table II). All three infections were characterized by symptoms of up-

per respiratory infection and by mild wheezing. During the following year (Table III), 16 children were infected with coronavirus OC38-43, none more than once. Of the ten single infections, all were symptomatic, with seven acute exacerbations of wheezing (two of which required intravenous therapy) and three episodes of pneumonia.

**Other viruses.** Adenovirus isolates were all of type 1 or type 2. Although mild or asymptomatic infections were common, in individual cases adenovirus infection of either type was associated with major acute illness. One child developed severe wheezing in association with both a rise in adenovirus complement-fixing antibody titer and recovery of *Mycoplasma pneumoniae* from the throat. Extensive bilateral pneumonia was seen in one girl who developed an 8-fold rise in complement-fixing antibody to adenovirus.

Although infections with parainfluenza virus type 1 and 3 were not uncommon, the



impact of these viruses was not as marked as those of respiratory syncytial virus, parainfluenza 2, and coronavirus OC38-43. Parainfluenza 3, during the first year of the study, was consistently associated with wheezing. However, parainfluenza 1 infection was rarely a significant problem during either year.

**Bacterial infection.** For the purpose of this study *Hemophilus influenzae*, pneumococcus,  $\beta$ -hemolytic streptococcus, *Staphylococcus aureus*, and the enteric gram-negative bacilli were considered potential bacterial respiratory pathogens. These organisms were recovered frequently from the respiratory tract of children both during and in the absence of wheezing. The percentage of recovery found in the first year is seen in Table V and shows no correlation with wheezing illness. In spite of the lack of such correlation, many children were treated with antibiotics at the time of acute respiratory illness. The number of infections with any given virus was too small to obtain meaningful information on viral-bacterial synergism.

**"Medication score" tracings in individual children.** The course of recurrent obstructive airway disease was variable in many of the children, and evaluation of acute episodes was often difficult. Examples of five medication score tracings of children who maintained a stable bronchodilator regimen in between acute attacks are shown in Fig. 3, with pertinent virologic data superimposed. It is clear that certain wheezing episodes were associated with viral infection and certain ones were not. Asymptomatic (i.e., nonwheezing) infections are also illustrated.

#### DISCUSSION

This study demonstrates a remarkable temporal association between respiratory virus infection and acute wheezing illness in young children hospitalized with recurrent reversible obstructive airway disease. During the study period 58 of 139 separate wheezing attacks (42 per cent) were associated with respiratory virus infection. Wheezing was almost always observed during respiratory syncytial virus infection (24 of 25 cases) and was found to a somewhat lesser extent dur-

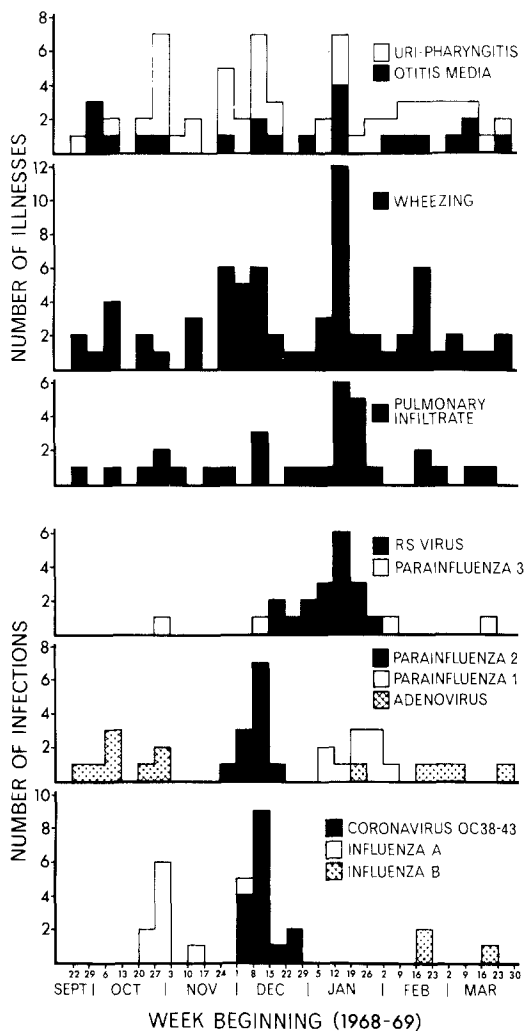


Fig. 2. Respiratory symptoms and illness in 20 asthmatic children in relation to respiratory viral infections (by weeks, 1968 to 1969).

ing infections due to parainfluenza viruses, coronaviruses, adenovirus, and influenza B. Indeed, the only virus which appeared to infect without ever inciting wheezing was influenza A<sub>2</sub>/Hong Kong.

Our study was not designed to prove by statistical methods a causal relation between virus infection and acute wheezing illness. Nevertheless, the nonstatistical evidence points strongly toward the concept that infection by certain viral species triggered attacks of acute wheezing in these children. This evidence is of two kinds. First, certain children, who were remarkably symptom free between acute attacks, developed clearly de-

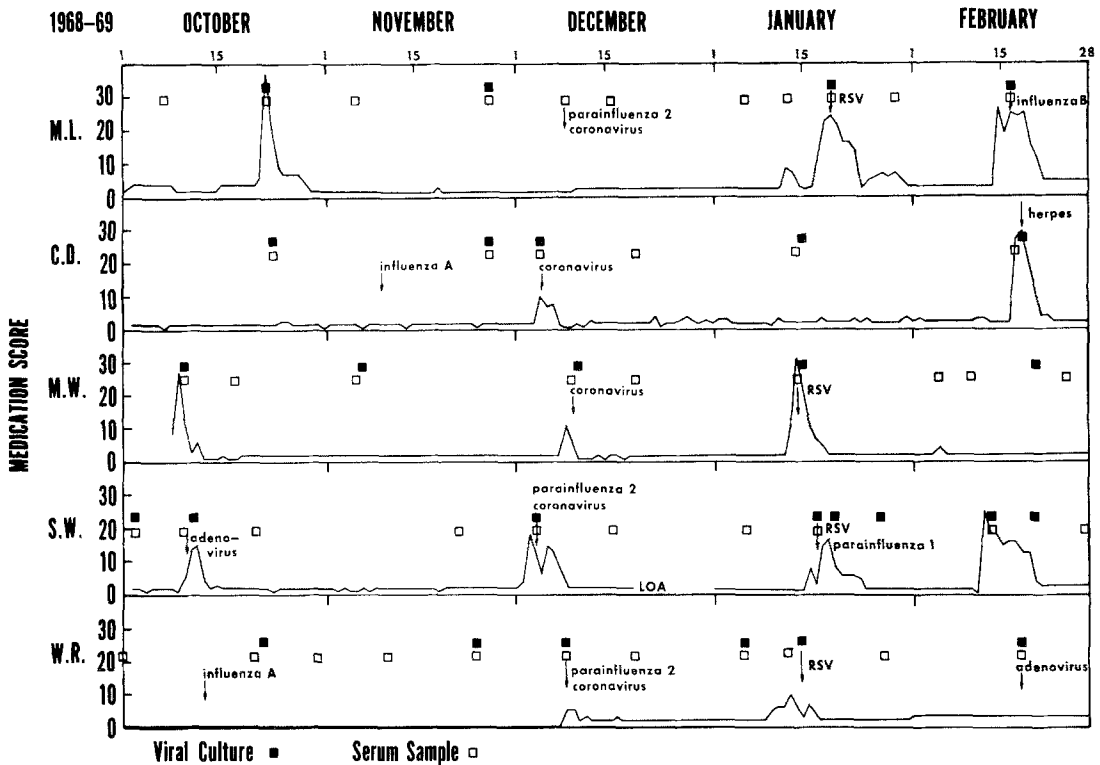


Fig. 3. Daily medication scores of five asthmatic children in relation to respiratory viral infection.

Table V. Association of "pathogenic" bacteria with wheezing in 12 asthmatic children (1967 to 1968)

Time of culture	Total No. cultures	No. of nasopharyngeal or throat cultures positive for indicated organism (% positive)				
		<i>Pneumococcus</i>	<i>H. influenzae</i>	<i>β-Hemolytic streptococcus</i>	<i>S. aureus</i>	<i>Enteric bacilli</i>
Wheezing	65	17 (26%)	21 (32%)	4 (6%)	12 (18%)	17 (26%)
Nonwheezing	178	43 (24%)	66 (37%)	13 (7%)	34 (19%)	37 (21%)

finer wheezing coincident with upper respiratory disease and viral infection (Fig. 3). Second, infection with certain respiratory viruses was frequently associated with wheezing, whereas with other viruses the relationship was infrequent or not observed at all. For example, in all 17 instances where respiratory syncytial virus was recovered, and in 7 of 8 infections identified by serologic methods, acute wheezing occurred. This was in striking contrast to influenza A infection, where none of 11 infections was temporally associated with acute wheezing. Other viruses

were intermediate in their capacity to cause obstructive symptoms. In these instances, individual children appeared to react differently to infection by the same virus. The factors involved in this discriminatory behavior are not known.

There is only a single previous report which attempts to link specific viral or mycoplasmal respiratory infections with exacerbations of wheezing in individuals with recurrent reversible obstructive airway disease.<sup>5</sup> In this study 136 children with acute wheezing were sampled in an outpatient clinic setting.

Only four viruses were recovered, two adenoviruses and two agents which were not characterized. However, using serologic techniques the authors were able to conclude that the fraction of wheezing attacks which might have been triggered by respiratory infection was about one third of the total, a proportion only slightly lower than that found in our survey.

In that report respiratory syncytial virus was a relatively uncommon pathogen, and influenza A<sub>2</sub> (not Hong Kong) was quite common. There have been three earlier descriptions of acute wheezing in asthmatic children infected with influenza A<sub>2</sub>,<sup>15-17</sup> all from the late 1950's when "Asian influenza" was epidemic. The Hong Kong strain of influenza A<sub>2</sub> produced no wheezing in our study, and appeared in this respect to be quite different from the earlier A<sub>2</sub> variant, and from respiratory syncytial virus, parainfluenza 2, and coronaviruses. Further studies are needed to confirm this finding, since the number of infections was small.

The coronaviruses are RNA-containing, membrane-enveloped viruses which are widely distributed in nature. In human adults they have been associated with 5 to 15 per cent of common colds. Previous attempts to associate coronavirus infection with lower respiratory illness in children have failed.<sup>11</sup> The association of infection with wheezing and pulmonary infiltrates, in addition to upper respiratory illness, in young asthmatic children therefore represents a possible extension of the pathogenic range of these organisms. On the other hand, because no virus recovery efforts were made, and because the number of children studied was small, this conclusion must remain tentative.

It is not clear by what mechanism respiratory viral infections might cause wheezing in asthmatic children. Virus infections are associated with wheezing illness under a number of diverse conditions. Certain of these conditions have been studied in some detail, and the disease mechanisms involved, both hypothetical and proved, are of interest and probable relevance to the findings in this study.

Acute bronchiolitis is a self-limited obstructive pulmonary disease occurring usually in children under the age of two years and most often during the first six months of life. The role of viruses in the etiology of acute bronchiolitis has been demonstrated beyond doubt by the careful epidemiologic studies of Beem and associates<sup>18</sup> and Chanock and associates.<sup>19</sup> Many respiratory viruses have been implicated as causal agents; these include parainfluenza 3, influenza, adenovirus, and, most frequently, respiratory syncytial virus. Although the epidemiology of this disease has been examined in great detail, the pathogenesis of wheezing in viral infection of the lower respiratory tract remains a matter of conjecture.

Because bronchiolitis is most common during the first six months of life, when bronchioles would be readily blocked by mucosal inflammation or proliferation, a mechanical process has been evoked by some to explain the pathogenesis of obstruction.<sup>20</sup> The predominance of respiratory syncytial virus infection can be explained, according to this hypothesis, by the frequency with which all types of lower respiratory tract illness are caused by this virus during early infancy.<sup>19</sup> The occurrence of bronchiolitis rather than pneumonia in the individual patient might be the result of a milder infection which did not spread from the mucosal surfaces into the interstitium.<sup>21</sup> Certain animal models tend to support this hypothesis.<sup>22</sup>

Other hypotheses invoke immunologic hypersensitivity in the pathogenesis of acute bronchiolitis and are therefore particularly pertinent to the findings in this study. Gardner and associates<sup>23</sup> have pointed to the presence of globulins, along with viral antigen, in the bronchiolar wall as detected by immunofluorescence of frozen sections obtained from fatal cases. They have hypothesized that an earlier "sensitizing" respiratory syncytial virus infection must precede an episode of bronchiolitis due to this organism. In support of this argument, they have presented evidence that respiratory syncytial virus infection in the neonatal period produced a characteristically mild disease.<sup>24</sup>

Additional evidence for an immunologic mechanism in at least some cases of bronchiolitis has emerged from studies of children who received a highly antigenic, inactivated respiratory syncytial virus vaccine. Recipients of the vaccine, on subsequent exposure to respiratory syncytial virus in the community, developed more severe bronchiolitis more frequently than unvaccinated control subjects.<sup>25-28</sup> Kim and associates<sup>26</sup> suggested the possibility of an Arthus-toxic complex (Gell and Coombs type 3) immunologic injury in these cases of vaccine sensitization. Chanock and associates<sup>29</sup> have invoked the same explanation for the occurrence of acute bronchiolitis in the otherwise normal young infant, when infection occurs in the absence of secretory antibody but in the presence of circulating (maternally derived) IgG antibody.<sup>29</sup> However, Fulginiti and associates,<sup>25</sup> recalling the anomalous "atypical" disease in recipients of killed measles virus vaccine, felt that delayed hypersensitivity (Gell and Coombs type 4) was also a possible pathogenic mechanism in severe postvaccine respiratory syncytial virus illness.

The severe postvaccine bronchiolitis may have particular relevance to the apparent pathogenicity of respiratory syncytial virus in asthmatic children. In a 4 year follow-up study, Eller and associates<sup>30</sup> reported that the development of asthma or other major allergy was significantly more common in vaccinees with severe postvaccine respiratory syncytial virus illness than in those without.

Further evidence for the possibility of some nonmechanical, and possibly immune, mechanism in acute bronchiolitis has come from follow-up studies of children presenting with this clinical syndrome. Several investigations have pointed to a high incidence of family and personal allergy and an increased probability of recurrent wheezing in children with acute bronchiolitis. Certain studies,<sup>31-36</sup> performed without the benefit of modern tissue culture techniques, traced patients who came to notice because of an episode of acute bronchiolitis in early childhood. It was found that 30 to 50 per cent of such children had further recurrent wheezing episodes. Many of

these children would later be labeled "asthmatic." The individuals who did have recurrent obstructive airway episodes had a higher incidence of family and personal atopy and eosinophilia in blood or respiratory secretions than those who did not have wheezing episodes again.

These observations have been corroborated by studies in confirmed viral acute bronchiolitis. Freeman and Todd<sup>37</sup> examined the problem retrospectively; they observed that infants and children who wheezed with proved respiratory virus infections were more likely to develop major allergy or "asthmatic bronchitis" than those who did not. However, those who wheezed with respiratory syncytial virus or adenovirus infection were less likely to develop atopic illness than those who wheezed with parainfluenza virus infections.<sup>38</sup> This view was supported by the studies of Simon and Jordan<sup>39</sup> who found a lower incidence of eosinophilia and "allergic" family history in children with respiratory syncytial virus-associated bronchiolitis than in children who had clinical bronchiolitis apparently due to other viral or nonviral causes. Rooney and Williams<sup>40</sup> observed recurrent wheezing following proved respiratory syncytial virus bronchiolitis in 56 per cent of observed patients. Thus, although there is disagreement about details and a distinct lack of adequately controlled studies, most investigators would accept the idea that bronchiolitis associated with virus infection is related in some children to recurrent wheezing, and that it may at times represent what would be called clinically an asthmatic attack in a young infant or child.

Allergy to infectious agents has been a popular concept in explaining the presence of recurrent obstructive airway symptoms in individuals who show little or no reaginic skin test sensitivity to common "extrinsic" allergens. On the other hand, attempts to demonstrate the importance of bacterial allergy in asthmatic individuals have been generally unsuccessful.<sup>2</sup> Attempts to desensitize by means of bacterial vaccines have likewise been of questionable value.<sup>1</sup> Indeed, an explanation for occasional clinical successes

with bacterial vaccines may have emerged from the recent demonstration that some commercially available bacterial vaccines induce interferon in mice.<sup>41</sup> It is hypothesized that these vaccines might by this means prevent respiratory viral illness.

Thus immunologic injury, on the basis of a type 1 (reagin-mediated), type 3, or even a type 4 mechanism, represents a possible explanation for the findings in this study. On the other hand, nonimmunologic factors, acting alone or in concert with immunologic factors, must also be considered. Szentivanyi<sup>42</sup> has proposed a theory of asthma in which the structure or function of beta adrenergic receptors in the airway is defective. In experimental animals in which beta adrenergic blockade has been induced a heightened sensitivity to histamine occurs. Partial beta adrenergic blockade is thought to exist in "atopic" individuals, and it is possible that viruses might act to aggravate the blockade and thus induce wheezing as a result of increased sensitivity to histamine or other agents released during an antigen-antibody reaction in the airway. There is evidence of increased sensitivity to inhalation of mecholyl (an analogue of acetylcholine) in asthmatic patients following administration of influenza vaccine<sup>43</sup> and during upper respiratory infection.<sup>44</sup> It is clear that further investigation is required to better define the effect of viral infection on the beta adrenergic system in normal and "atopic" subjects.

Our data fail to define a mechanism for the airway obstruction observed. However, it is curious that respiratory syncytial virus, which has a particular propensity to cause bronchiolitis, and which has apparently been involved in vaccine-induced hypersensitivity, should have been so clearly associated with acute wheezing in these children. But it remains uncertain whether the pathogenetic process illustrated in this study is similar or identical to that involved in bronchiolitis during infancy or following killed vaccine. Some episodes of viral bronchiolitis probably represent early attacks of airway obstruction in children constitutionally predisposed (perhaps by their atopic nature) to develop asthma,

and therefore do not differ significantly from the wheezing attacks described here.

In spite of our uncertainty about mechanisms, it appears clear from these studies that viral respiratory infections trigger a substantial proportion of wheezing attacks in young asthmatic children, and that prevention of such infections, through vaccines or chemotherapy, would significantly improve their clinical status.

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