The Precipitation of Asthma by Upper Respiratory Infections*

William W. Busse, M.D.

Upper respiratory tract infections precipitate wheezing in many asthma patients. Understanding the mechanism of these attacks is important both in terms of medical management and providing insight into the pathogenesis of asthma itself. I will describe some important contributions which have helped us better understand the relationship between upper respiratory infections and asthma.

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The Epidemiology of Respiratory Infections and Asthma

Between 1967 and 1969, McIntosh and co-workers prospectively studied 32 young children aged 1 to 5 years with asthma hospitalized at the National Jewish Hospital in Denver. The etiology of each acute upper respiratory infection (URI) was carefully evaluated by culturing for the presence of virus and bacteria along with serologic testing for viral antibody titers. Each exacerbation of asthma was documented by physical examination and changes in bronchodilator medication. During the 2-year study, the 32 children had 102 confirmed viral respiratory infections and 139 episodes of wheezing. Fifty-eight episodes of wheezing occurred in association with a viral respiratory infection. Of the virus identified, respiratory syncytial virus (RSV) infection was the most prevalent and most likely to provoke asthma. Haemophilus influenzae, pneumococcus, β-hemolytic streptococcus, and Staphylococcus aureus were also recovered from the respiratory tract but their presence did not correlate with an attack of asthma.

In a subsequent prospective outpatient study from our institution, 16 children aged 3 to 11 years were closely observed from October 1971 to May 1972. These children formed a highly selective group, as all had a history of 4 or more asthma attacks associated with respiratory illnesses during the previous year. Furthermore, to prevent confusion, a patient was excluded if winter-time allergic reactions existed which might provoke asthma. Detailed clinical records were maintained along with biweekly examinations, and patients had cultures taken for virus by a nurse. During an asthma exacerbation or a URI, bacteria and virus cultures were obtained more frequently, and the asthma symptoms were carefully quantitated.

Our 16 patients experienced 61 episodes of asthma, 42 of which were coincident with a symptomatic respiratory infection; 24 of these were confirmed to be of viral etiology. Rhinovirus was the virus most frequently isolated from patients with episodes of increased wheezing. During periods of asymptomatic virus shedding, asthma was not precipitated. Furthermore, only 1 episode of wheezing coincided with a bacterial infection.

Although not nearly as striking as that found with children, a relationship between viral respiratory infections and the provocation of asthma also was shown in epidemiologic studies in adults. Another study from our institution examined both children and adults. Respiratory viruses were more frequently identified during asthma attacks in children under 10 years old than in adults. The 8 adult participants in this investigation had only 3 virus isolates during times of increased wheezing. Many factors contribute to the difficulty of identifying respiratory virus in adults. Perhaps the most important is that episodes of asthma in adults are less sharply delineated, and therefore the timing for virus cultures is not as accurate. This conclusion is underscored by a study of Hudgel and co-workers, who evaluated 19 adult patients with chronic asthma over 15 months. Seventy-six exacerbations of asthma were evaluated. Only 8 of these 76 episodes (11 percent) documented a viral etiology. Although respiratory virus precipitates asthma in adults, the relative frequency is lower and more difficult to document than in
children.

Bacterial respiratory infections do not cause attacks of asthma. Berman and co-workers\(^6\) did transtracheal-aspiration cultures on 27 adult asthma patients during a respiratory infection. Bacteria cultured from transtracheal aspirates was sparse and did not correlate with the clinical illness. More important, transtracheal isolates from normal subjects without respiratory infection yielded a similar degree of bacterial colonization. From this and the other studies cited, there is little support for bacterial respiratory infections as a precipitant of asthma.

A number of important conclusions can be drawn from these studies. First, symptomatic respiratory infections which provoke asthma in both children and adults are likely to be viral in origin; however, this association is more readily apparent in children younger than 10 years old. Second, many viruses can provoke asthma, and the most prevalent organism varies with the patient's age (Table 1). Third, asymptomatic virus shedding or mild URIs are unlikely to provoke asthma. Finally, there is no evidence that bacterial respiratory infections cause wheezing.

Not only do viral URIs provoke asthma, but also the development of asthma may be a consequence. This unique linkage is best illustrated in children recovering from bronchiolitis. A portion of children with bronchiolitis recover with sequelae and have no further problems. In many others the initial bronchiolitis bout is followed by recurrent episodes of wheezing with subsequent viral respiratory infections—in 30 to 50 percent. The patients most susceptible to recurrent episodes of wheezing are offspring of allergic parents. The mechanism by which bronchiolitis usher in recurrent virus-induced asthma is largely unresolved, but undoubtedly assumes a critical part in the asthma pathogenesis puzzle.

**The Consequence of Viral Respiratory Infection on Airway Function**

To better understand virus-induced asthma, it is worthwhile evaluating lung function and airway reactivity in normal subjects during URIs (Table 2). Studies in normal persons are important because subtle effects of a viral URI on airway function in asthma might easily be overlooked in the presence of advanced disease. Furthermore, the study of hyperreactivity in asthma is complicated by drug treatment, hypertrophy and hyperplasia of airway smooth muscle, and variable degrees of pulmonary obstruction, each of which makes it difficult to estimate virus-induced changes.

An early study by Pickens and colleagues\(^7\) evaluated 12 healthy subjects who had a common cold. Throughout the study, all the patients had normal measurements of flow rates and airway resistance. However, four patients had a striking change in the frequency dependence of compliance, which lasted 4 to 8 weeks after the acute infection. The dysfunction in small airway tests was subtle and did not cause clinical symptoms.

Hall et al\(^8\) assessed airway function in 13 college-aged students with documented, uncomplicated influenza virus type A infection. Ten of 13 subjects tested had severely abnormal frequency dependence measurements of airway resistance. Retesting showed that these changes persisted in some patients for 3 to 5 weeks. It was also found that the increase in pulmonary resistance was mild and confined principally to measurements of peripheral airway function.

In yet another study, Blair and associates\(^9\) inoculated normal volunteers with live rhinovirus. Five of 8 subjects became infected and had increased frequency dependence of compliance at the time of the respiratory illness. These abnormalities returned to baseline 2 weeks later.

There is a rather consistent pattern which emerges from these studies of normal subjects. The uncomplicated viral URI produces pulmonary obstruction limited mainly to smaller airways. The airway changes are subtle but persist well beyond the clinical illness. In asthma, because there is underlying airway obstruction, the patient appears to be more susceptible to the consequences of the viral URI and has symptomatic or severe wheezing.

**Viral Respiratory Infections Enhance Airway Reactivity**

Empey and co-workers\(^10\) monitored airway reactivity in 12 young normal subjects with a clinical, uncomplicated URI. Airway reactivity was measured by a change in resistance to an aerosol administration of histamine. This response was measured in the URI patients and compared to 11 matched controls without a cold. The subjects with a cold had a significantly greater increase in airway resistance to aerosol histamine (218 ± 54.6 percent) than did the controls (30.5 ± 5.5 percent). Although the URI symptoms disappeared within a week, the airway hyperreactivity to histamine continued for 6 weeks in some subjects.

Additional experiments by Empey et al\(^11\) furnished insight into the mechanism of virus-induced airway hyperreactivity. When the URI patients were pretreated with aerosolized atropine, the histamine challenge did not change the airway resistance. The atropine protection is strong presumptive evidence that the virus-associated airway reactivity was mediated by a reflex response, a point which will be discussed further.

Respiratory syncytial virus (RSV) is a major pathogen of childhood bronchiolitis and, moreover, provokes asthma in youngsters. Hall et al\(^12\) prospectively evaluated 10 adults, employees of an infants' ward, who were infected with RSV.

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**Table 1—Viral Respiratory Infections Which Precipitate Asthma**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Parainfluenza</th>
<th>Rhinovirus</th>
<th>RSV</th>
<th>Adenovirus</th>
<th>Parainfluenza virus</th>
<th>M. pneumoniae</th>
<th>M. pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young Children</td>
<td>RSV</td>
<td>Rhinovirus</td>
<td>M. pneumoniae</td>
<td>Adenovirus</td>
<td>Parainfluenza virus</td>
<td>M. pneumoniae</td>
<td>M. pneumoniae</td>
</tr>
<tr>
<td>School-aged</td>
<td>RSV</td>
<td>Rhinovirus</td>
<td>M. pneumoniae</td>
<td>Adenovirus</td>
<td>Parainfluenza virus</td>
<td>M. pneumoniae</td>
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<td>Adolescence</td>
<td>RSV</td>
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<td>M. pneumoniae</td>
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**Table 2—The Consequence of Viral Respiratory Infection on Airway Function in Normal Subjects**

| Pulmonary obstruction occurs during viral URIs and involves principally small airway function |
| Small airway obstruction from viral infections will persist for weeks beyond the clinical symptoms |
| Airway hyperreactivity develops in some patients during viral URIs |

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Table 3—Proposed Mechanisms of Virus-induced Asthma

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Respiratory viruses cause airway inflammation to sensitize rapidly adapting sensory fibers of the vagus. Reflex bronchoconstriction follows airway stimulation.</td>
<td></td>
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<tr>
<td>Respiratory viruses diminish β-adrenergic responsiveness.</td>
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<tr>
<td>Respiratory viruses stimulate the production of virus-specific IgE antibody.</td>
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<tr>
<td>Respiratory viruses and products of virus-infected cells (interferon) enhance mediator release.</td>
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</table>

All 10 subjects were symptomatic during the RSV infection and had a cough which lasted at least 1 week. Four weeks later, almost all patients were asymptomatic except for mild shortness of breath, which also gradually resolved. Pulmonary function tests on these 10 patients demonstrated increased airway resistance for at least 5 weeks after the onset of the RSV illness. Furthermore, all subjects had an exaggerated increase in airway resistance with the inhalation of a cholinergic agonist, carbachol. The airway hyperreactivity to carbachol was still present 8 weeks after the acute infection.

Mechanisms of Virus-induced Asthma

Sensitization of Vagus Afferent Sensory Fibers

Empey et al. found a transient bronchial hyperreactivity to an aerosol of histamine in normal individuals with a viral URI (Table 3). In addition, the threshold for citric acid to stimulate cough was lowered during the URI. Both responses are indicators of airway hyperreactivity and could be prevented by atropine therapy. The protection with atropine strongly implies that a vagal-mediated reflex is involved in virus-associated airway hyperreactivity. To explain their observations, the authors postulated that respiratory viruses damage the bronchial epithelium to sensitize rapidly adapting sensory vagus fibers found in the airways. These afferent sensory receptors are located principally in the subepithelium of larger airways. A wide variety of stimuli (eg, citric acid or histamine) is able to activate the sensitized afferent receptors to elicit a vagus-mediated reflex bronchoconstriction. The airway damage from respiratory viruses requires weeks to heal. The length of time required for epithelial healing corresponds to the persistence of airway irritability.

Development of Virus-specific IgE Antibody

In a study of 42 infants and youngsters with respiratory illnesses from respiratory syncytial virus, Welliver and coworkers found IgE attached to exfoliated nasopharyngeal epithelial cells. Cell-bound IgE appeared in 70 to 80 percent of all patients during the first 10 days of illness. By examining the relationship of the particular clinical illness to the frequency and persistence of cell-bound IgE, an interesting pattern emerged. All of the patients with bronchiolitis or asthma had cell-bound IgE in their nasal secretions when tested seven to 20 days into the illness. In contrast, only 33 percent of patients with pneumonia or URI had detectable cell-bound IgE at the same time. Throughout the study, patients with bronchiolitis or asthma continued to have a persistently higher frequency of the IgE marker. Moreover, patients with higher levels of cell-bound IgE were more likely to have a family history of wheezing.

In a subsequent study Welliver et al. evaluated an additional 79 children, all younger than 12 months, with documented RSV bronchiolitis. The clinical pattern of illness in these children could be divided into 4 groups: (1) upper respiratory tract illness, (2) pneumonia without wheezing, (3) pneumonia and wheezing, and (4) wheezing (bronchiolitis). Nasal secretions from each patient were measured for IgE-specific antibody to RSV and histamine. When RSV-IgE antibody titers were compared with the patient's clinical illness, the following association was apparent. First, IgE titers to RSV were highest in patients with airway obstruction, pneumonia/wheezing, or wheezing. Furthermore, patients with the highest RSV-IgE titers also had the lowest arterial PO2 values. One additional observation found an inverse correlation between the concentration of histamine in the nasal secretions and the lowest arterial PO2. That is, high nasal histamine concentrations were more likely to be found in patients with low arterial PO2.

At present, the interpretation of these exciting findings relevant to the pathogenesis of virus-induced asthma is speculative. Clearly, RSV viruses elicit the production of specific IgE antibody. It is possible that newly formed IgE antibody will attach to mast cells and then interact with the RSV antigen. The IgE-RSV interaction can stimulate mediator release to cause airway obstruction. At the present, it is only conjecture that the IgE-specific-antibody causes histamine release. However, it is important to emphasize that mediator release by itself does not cause asthma. The coexistence of conditions, such as bronchial inflammation, may create airway vulnerability to vasoactive hormones. The importance of the Welliver studies is the clear demonstration that an IgE antibody to viruses can develop during respiratory illness.

Respiratory Viruses Diminish β-Adrenergic Responsiveness

It has been nearly 2 decades since Szentivanyi proposed that a major factor contributing to the pathogenesis of asthma is an imbalance in the autonomic nervous system control of airway smooth muscle; specifically, a diminished β-adrenergic responsiveness. Beta-adrenergic responsiveness is diminished in some patients with asthma. Indeed, an attack of asthma may follow the administration of β-adrenergic antagonists such as propranolol to asthmatic patients. Therefore, if respiratory viruses compromised β-adrenergic tone in the airways of asthmatics, increased wheezing would be a likely consequence. We have used leukocytes isolated from asthma patients as a model to evaluate β-adrenergic function. Specifically, we have examined the granulocyte response to isoproterenol, which inhibits lysosomal enzyme release via the AMP system, as a measurement of β-adrenergic function in asthma. In asthma, this granulocyte isoproterenol response is diminished and further impaired during a viral URI which provokes asthma. Thus, we have speculated that if similar changes occur in the β-adrenergic function of airway smooth muscle, increased bronchospasm would result.

To further define this relationship, we incubated isolated human granulocytes with live respiratory viruses and then evaluated the cell's response to isoproterenol. Virus-treated granulocytes were less responsive to isoproterenol. Because both rhinovirus and influenza virus, which are associated
with clinical episodes of asthma, were used in these experiments, our observations may have direct clinical application. The application of our studies to clinical asthma is noted by the following reasoning: Airway inflammation is a major contribution to obstruction in severe asthma of any cause and neutrophils undoubtedly play a role in this function. Because catecholamines can reduce inflammation by inhibiting lysosomal enzyme release, a viral impairment in this β-adrenergic function can translate into increased lysosome release with tissue inflammation and, therefore, asthma.

**The Effect of Respiratory Viruses on Mediator Release and Basophil Function**

Mediator release and events which regulate this process are undoubtedly pivotal in the pathogenesis of asthma. Although the pulmonary mast cell is biologically the most relevant cell in this process, the release of histamine from basophilic leukocytes has proved a reliable and instructive model to study immediate hypersensitivity reactions. To evaluate the effects of respiratory viruses on basophil histamine release, Ida et al. conducted the following experiments. Isolated human leukocytes were incubated with herpes simplex virus, influenza virus type A, and adenovirus. Following virus treatment, basophil histamine release was enhanced. The degree to which this enhancement occurred related to the degree of virus infectivity.

A similar degree of enhanced basophil changes in leukocyte release occurred when inactivated virus was used in the incubation mixture. Most interestingly, Ida et al. found that basophil mediator release enhancement paralleled the production of interferon which occurred during the virus incubation. Moreover, a similar enhancement in leukocyte histamine release occurred if exogenous interferon was substituted for virus in the incubation mixture. We have found similar enhancement in leukocyte histamine release to ragweed antigen E following an incubation with influenza virus type A or interferon. Thus, not only may virus directly contribute to increased asthma, but also the generation and release of factors from virus-infected cells will enhance this process. The role of other factors in this process awaits further study.

Because mediator-releasing cells can have a profound effect on airway tone, recruitment of these cells to sites of infection could also promote asthma. Lett-Brown and coworkers incubated leukocytes with a parainfluenza influenza virus. Following the virus incubation, leukocyte chemotaxis was measured to a C5 peptide of complement or a lymphocyte-derived chemotactic factor. Interestingly, only the basophils from the virus-treated leukocyte mixture had enhanced chemotaxis. Furthermore, if interferon was substituted for virus, basophil migration was likewise enhanced. Although these observations were performed in vitro, if similar conditions prevailed during a viral infection, basophil accumulation in the airway may be promoted. If more basophils were present in the airways, the quantitative generation of smooth muscle contractile mediators would be facilitated; as a consequence, a more severe attack of asthma may result. The multiple effects of a respiratory virus on basophil function are summarized in a hypothetic scheme in Figure 1.

**AN ANIMAL MODEL FOR VIRUS-INDUCED ASTHMA**

Until recently, an animal model was lacking in which virus-induced changes in lung function could be systemically examined. To this end, we have developed and used the parainfluenza-3-infected, ovalbumin-sensitized guinea pig. Guinea pigs actively sensitized with ovalbumin were inoculated with parainfluenza-3 4 days before performing in vitro pharmacologic studies on tracheal and bronchial smooth muscle. The airway segments were contracted with cumulative doses of ovalbumin in the presence and absence of a β-adrenergic receptor agonist, which reduced the contractile response to ovalbumin. Although the viral infection did not alter the dose-response contractions with ovalbumin, the magnitude of β-adrenergic inhibitory effects was smaller in airway segments obtained from virus-infected animals. Blockade by virale infection of the inhibitory effects of the β agonist was overcome by increasing the agonist concentration. In addition, the β agonist did not alter the airway smooth muscle contractile response to histamine or carbachol. These studies demonstrate that the infection of

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**Figure 1.** Respiratory viruses can interact with the lymphocyte system to produce virus-specific IgE antibody. Theoretically, the virus-specific IgE will sensitize basophils and mast cells. A subsequent interaction of cell-bound IgE with the respiratory virus causes mediator release. This response can be compounded as either virus or the product of virus-infected cells, interferon, enhances mediator release. Histamine release can produce airway obstruction directly or increase bronchial hypersensitivity by producing airway inflammation.
the guinea pig with a respiratory virus caused a selective blockade of the β-adrenergic-mediated inhibition of antigen-induced contraction of airway smooth muscle. One plausible explanation is that the respiratory virus alters the airway mast cell's inhibitory response to a β agonist, thus ablating normal catecholamine suppression of mediator secretion. This conclusion awaits further confirmation. Moreover, we found that the intrinsic contractile and relaxing airway smooth muscle response is unaltered by virus. In studies to date, we have identified the major site of the virus effect to be on cells, eg, mast cells, which are critical in regulating bronchial smooth muscle tone.

**Summary**

A number of important mechanisms have been identified by which viruses can provoke asthma. From the data available, there does not appear to be one single mechanism available to explain virus-induced asthma. The relationship between viral URIs and asthma is complex and involves many organ systems: airway epithelium, autonomic nervous system control, and the immediate hypersensitivity system. Identifying the effects of respiratory viruses on airway function remains an important undertaking as we try to better understand and control this precipitant of asthma.

**References**


**Exercise-Induced Asthma**

Charles Scoggin, M.D., F.C.C.P.*

Many individuals with reversible airways dysfunction or asthma are troubled by symptoms of shortness of breath, cough, and wheezing when they attempt to exert themselves. These complaints are particularly frequent when exercising in environments that are both cold and dry. Physiologically, this abnormality is characterized by a development of obstructive airways dysfunction on pulmonary function testing. This article will focus on an overview of the problem, the physiology of exercise-induced bronchospasm (EIB), and the management of the condition.

**Overview of the Problem**

It is probable that all persons with asthma are sensitive to development of EIB. It is characterized as a response to exercise in which there is a fall in the forced expiratory volume in the first second (FEV₁) or peak expiratory rate (PEFR) greater than 10 percent of preexercise values. Typically, the symptoms begin six to ten minutes after beginning exercise and are characterized by chest tightness, shortness of breath, wheezing, cough, and occasionally even stomach-ache. A second phase of EIB, which is usually the most severe, occurs after the exercise. When unaffected persons are recovering from the effects of exercise, those with EIB

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