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# Respiratory Infection and Airway Reactivity

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Pediatricians and internists share common clinical observations: patients with recurrent wheezing or asthma frequently have an antecedent history of severe respiratory infections. Several lines of evidence support these clinical impressions. Epidemiological studies have implicated viruses and mycoplasma pneumonia in the etiology of acute wheezing illnesses in children and adults.<sup>14, 18, 25</sup> Data from clinical studies suggest a relationship exists between the viral and mycoplasma pathogens implicated in upper respiratory illness and abnormalities in lower airway bronchomotor reactivity.<sup>1, 10, 22</sup> Finally, it has been suggested that the same infections that produce acute increases in airway reactivity also alter host defense mechanisms and lead to the development of allergic sensitization.<sup>11</sup>

These observations raise two important questions. First, what anatomic, physiologic, or immunologic alterations occur during respiratory infection that acutely increase airway reactivity? Second, is there any relationship between these acute infectious episodes and the development of sensitization of airways to bronchoconstrictor stimuli? This article will review the clinical data demonstrating the association of wheezing with respiratory infections, the changes in pulmonary functions that accompany these illnesses, and the physiologic alterations induced by infection that may produce both acute and chronic changes in lower airway reactivity.

## CLINICAL BACKGROUND

During the last decade a wealth of data demonstrating the association of wheezing and viral and mycoplasma infection has been reported. These findings have been made in diverse populations. McIntosh and associates<sup>25</sup> reported that 42 per cent of wheezing episodes in chronically hospitalized

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asthmatic preschoolers occurred during acute viral infection. Respiratory syncytial virus (RSV), parainfluenza type II, and coronaviruses were the most common identified pathogens. Minor and colleagues<sup>27</sup> found in a population of older asthmatics a similar occurrence of wheezing during acute viral illness. Rhinovirus of several different serotypes and influenza A were temporally associated with wheezing in this study. Henderson and coworkers<sup>14</sup> in a study of a general practice population showed that age and time of year were important variables in the occurrence of wheezing associated with respiratory infection. RSV was the predominant organism in infants and toddlers with a persistent but decreasing importance in older children. Rhinovirus and *Mycoplasma pneumoniae* were of increasing frequency in school-age children. There was a seasonal peak of wheezing with RSV in the mid-winter months in children less than 2 years of age and in October and November with *M. pneumoniae* in children over 5. The fall epidemic of wheezing in older children is significant in that it coincides with reports of peak admissions and emergency room visits for asthma noted during these months.<sup>3</sup> These data demonstrate that wheezing associated with respiratory infection occurs in all pediatric populations, regardless of whether severe hospitalized asthmatic children or children from a general practice are studied. Data suggesting that increased airway reactivity occur in adult individuals during viral respiratory infections, both "normal" adult as well as those with asthma and/or a history of atopy, will be reviewed below. No correlation has been found between the occurrence of wheezing and acute bacterial infections in either adult or pediatric populations.<sup>14,18,27</sup>

A question that frequently arises is whether the association between wheezing and acute respiratory illness might be explained by the fact that people with recurrent wheezing or asthma are more prone to infection. Minor and investigators<sup>26</sup> reported that individuals who had histories of wheezing demonstrated an increased incidence of viral infection when compared to their nonwheezing siblings. This increased rate of infection was related exclusively to the recovery of rhinoviruses. Tarlo and co-workers<sup>36</sup> in a study of asthmatics and their nonwheezing spouses found an increased number of symptomatic colds in the asthmatic population but a higher viral isolation rate and increased serological changes in the nonasthmatic spouses. Stempel and colleagues<sup>34</sup> found that the infection rate was the same for both the wheezing and nonwheezing population. The data of the latter two studies suggest that the incidence of infection may not be significantly different in individuals with a history of wheezing compared to those without.

## RISK FACTORS

Despite the fact that all individuals are exposed to the same common respiratory pathogens, the bronchopulmonary responses to these insults vary greatly. At least one predisposing factor that identifies subjects at risk to wheeze during these common respiratory infections has been reported. In the study by McIntosh,<sup>25</sup> 90 per cent of the patients that wheezed in their study were considered clinically atopic. In the report of Stempel et al.,<sup>34</sup> the

incidence of elevated IgE values in the wheezing study subjects was similar (85 per cent). Accordingly, the atopic state, as reflected by IgE elevation, may be predictive of a bronchospastic response to infection as well as to allergic stimuli.

The fact that not all individuals who wheeze with viral and mycoplasma infections have elevated IgE's raises several additional possibilities to account for this lack of relationship: (1) IgE is but one of several physiological pathways for the occurrence of wheezing with respiratory infection, (2) serum IgE may not reflect the presence of cell-bound IgE in various locations within the airway wall, and (3) IgE bears a serendipitous relationship to this association.

Welliver and co-workers<sup>41</sup> in a study of young children during RSV infection demonstrated that cell-bound IgE on nasopharyngeal epithelial cells persisted longer in those individuals with bronchiolitis or asthma as compared to an uncomplicated upper respiratory infection or pneumonia. This persistence of cell-bound IgE was found to be more common in children with a previous history of wheezing or with a family history of wheezing. Children who had prior episodes of bronchospasm did not have evidence of cell-bound IgE prior to the infection with respiratory syncytial virus. These data suggest a possible role for IgE bound to respiratory cells in the mechanism of acute wheezing during viral infections.

An increase in total serum IgE in the study subjects was not observed by Welliver. The explanation for this finding may relate to the time of the sera sampling relative to the acute illness. Studies by Bahna and co-workers<sup>2</sup> and Perelmutter and investigators<sup>28</sup> found serum IgE levels elevated in the first week after viral infection followed by significant depression for several weeks to months. Decreased IgE production in the convalescent phase of an acute viral illness may be explained by altered T cell responsiveness during viral illness.<sup>40</sup> Stempel and associates<sup>35</sup> have recently investigated a group of normal children and noted a seasonal variation in IgE. Total IgE values tended to be significantly lower in the spring after the winter respiratory disease season. These findings are consistent with those of Bahna and Perelmutter. However, no groups have documented specific serum IgE responses to viral antigens post infection.

What is the prognosis for a child with an acute episode of wheezing associated with respiratory infection? Does it predispose the child to subsequent pulmonary disease as an adult? Burrows and co-workers<sup>8</sup> in a retrospective analysis concluded that pediatric respiratory illness was a significant risk factor in the development of obstructive airway disease. Kattan and investigators<sup>20</sup> reported pulmonary function abnormalities in a group of 23 children who experienced bronchiolitis as infants after 10 nonwheezing, asymptomatic years. Loughlin et al.,<sup>23</sup> using exercise, and Gurwitz and co-workers,<sup>13</sup> using methacholine as stimuli, have shown that children with a history of croup in early childhood demonstrate enhanced airway reactivity for up to 8½ years after the initial illness. Both studies found no association between airway reactivity and atopy in their study groups.

Virus infections appear to induce transient increases in airway irritability in healthy, nonatopic adult subjects. Virus-induced airway hyperreactivity was first documented experimentally by Empey and co-workers<sup>10</sup> who

showed that normal adult subjects after upper respiratory viral infections demonstrated enhanced bronchial hyperreactivity after the inhalation of histamine diphosphate and citric acid. This exaggerated response could be blocked by the prior inhalation of atropine sulfate, and the authors suggested sensitization of rapidly adapting irritant receptors in airways could account for these findings. More recently, Aquilina and associates<sup>1</sup> reported that increased airway reactivity in subjects with viral upper respiratory infections could be induced employing exercise and cold air as a stimulus. This response was blocked by the preadministration of an oropharyngeal anesthetic (lidocaine), suggesting a pharyngeal locus for receptor sensitization.

The link between the relatively mild response seen in normal adults to virus infections — i.e., increased airway irritability — and that seen in infants (wheezing) is unclear. It is conceivable the more severe response in infants as compared to adults reflects the relative differences in effective cross sectional areas available for airflow in smaller airways. In particular, infants with proportionally less cross sectional area in these regions may be more vulnerable to virus-induced damage to the airway walls.<sup>17</sup> However, resolution of this problem awaits a clearer understanding of the control of bronchomotor tone in both infants and adults.

### POSSIBLE MECHANISMS OF VIRUS-ENHANCED AIRWAY REACTIVITY

It is difficult to assess the mechanisms by which viruses may induce airway hyperactivity because the normal control of bronchomotor tone is still poorly understood. This subject has recently been reviewed by Boushey and co-workers.<sup>7</sup> They suggest four mechanisms of airway hyperreactivity: (1) changes in baseline airway caliber, (2) increased smooth muscle reactivity, (3) sensitized vagal afferent neuroreceptors, and (4) increased airway mucosal “access” or hyperpermeability. The following discussion will focus on possible interactions between virus infections and these proposed mechanisms to account for bronchial hyperreactivity.

#### Pre-existing Airway Constriction

Airway flow resistance is inversely proportional to the airway radius to the fourth power. It has been suggested that the enhanced response to chemical agonists reflects the relatively large contribution of small but critical challenges in airway caliber induced by the noxious insult — e.g., viral infection.<sup>33</sup> Whether the reduction in airway diameter is a function of increased bronchomotor tone or intraluminal mucus and cellular debris is unclear and may vary with the insult. Virus infection conceivably may reduce cross-sectional diameter by either mechanism. For example, several lines of evidence suggest that the airway lumen, particularly in the smaller airways, may become occluded during or as a consequence of viral infections. First, histopathologic studies of virus infections in humans have shown extensive cytopathic changes in airway epithelium resulting in desquamation of the damaged and destroyed epithelial cells into the airway lumen.<sup>24</sup> Second, epithelial cell damage results in a loss of functioning ciliated cells, perhaps

contributing to decreased clearance of intraluminal products.<sup>29, 38</sup> Finally, the depth of the so-called "sol" layer, the liquid layer in which the cilia beat, appears important in the regulation of mucociliary clearance rates.<sup>21</sup> The volume and composition of the layer is regulated by active ion transport mechanisms located in airway epithelium. Although the nature of the transport mechanism varies among species and within airway regions in the lung, it appears that in the major bronchi sodium chloride and water are absorbed across the airway wall and that an intact epithelium is necessary for normal maintenance of this function.<sup>6</sup> Destruction of the epithelium barrier by virus agent would limit the generation of micro-osmolar gradients across this barrier that promote liquid absorption, raising intraluminal liquid volume, and depressing mucociliary clearance rates.

### Increased Smooth Muscle Reactivity

Pathological studies have shown no evidence of cytopathic changes in airway smooth muscle.<sup>29</sup> In addition, immunofluorescent studies of viral antigen have failed to show these antigens in the region of airway smooth muscle.<sup>15</sup> There are intriguing observations, however, that viruses may reduce beta receptor-mediated activity.<sup>7</sup> Because impaired beta-receptor activity has been reported in airway smooth muscle from antigen-sensitive dogs, it is conceivable that virus effects on beta-receptors in airway smooth muscle may occur.<sup>30</sup> Further, demonstration of the association of type I IgE-mediated sensitivity disease and changes in smooth muscle reactivity were suggested by a study by Ida et al.<sup>19</sup> They showed that a soluble factor with the properties of interferon enhanced the release of histamine from human peripheral leukocytes after challenge with ragweed antigen E or anti-gE. This suggests the involvement of chemical mediators in both virus-induced and antigen-induced asthma. Therefore, despite the lack of pathological data on the support of virus effects on airway smooth muscle, *in vitro* physiological studies to screen for abnormalities in smooth muscle from virus-infected animals in airway reactivity and relaxation appear warranted.

### Sensitized Vagal Afferent Neuroreceptors

One of the prevailing concepts as to the nature of the defect that induces airway reactivity is that of the "sensitized vagal efferent receptor."<sup>42</sup> The contribution of the vagal system to airway irritability has been documented by the ability of inhaled atropine or vagal section to block hyperreactive responses.<sup>37</sup> Despite the initial appeal of this hypothesis, a number of recent observations are not consistent with it, as originally described. For example, direct recordings of vagal afferent activity from dogs has shown that cholinergic agents, in contrast to histamine, do not induce irritant receptor activity. Since methacholine has been one of the traditional chemical agonists employed to demonstrate enhanced airway constriction in virus-infected individuals, it appears likely that this agonist must be working by other mechanisms than stimulating sensitized vagal afferent fibers. In addition, respiratory viruses have not demonstrated a tropism for neural structures *in vivo* or *in vitro*, nor have immunofluorescent studies shown virus antigens in regions of neural afferent receptors.<sup>32</sup> However, indirect effects on neural afferents induced by soluble mediators released in response to virus infection cannot be ruled out without more direct neurophysiological data.

## Airway Hyperpermeability

The airway epithelium normally forms the principal barrier that limits the movements of inhaled agents that are deposited on the airway surface to elements that control bronchomotor tone in the airway wall — i.e., neural afferents and/or smooth muscle. Insults that damage the airway epithelium, principally the tight junctions adjoining airway epithelial cells, accelerate the movement of chemical agonists deposited on the airway surfaces to these effector sites and induce enhanced constrictor responses.<sup>16</sup>

Respiratory viruses demonstrate a tropism for epithelial cells and produce cellular damage and destruction. Recent studies by Richardson et al.<sup>32</sup> have shown that movement of large molecules across the epithelial barrier is greatly increased consequent to a virus-enhanced disruption of the epithelium. In addition, these studies showed with ultrastructural techniques that afferent neural fibers in the epithelium appeared to be intact at the peak of virus infection but directly exposed to the airway lumen. Therefore, because of this finding, it appears possible that enhanced airway reactivity associated with virus infection, as demonstrated by inhaled histamine or methacholine challenge, may reflect the increased flow of these agonists across the airway mucosal surface to exposed vagal afferents and/or smooth muscle.

However, it must be emphasized that the hypothesis of enhanced airway reactivity to inhaled chemical agonists reflecting increased access or hyperpermeability of airway surfaces has not been critically tested. Experiments in other situations where airway hyperpermeability can be transiently induced — i.e., experimental allergic bronchoconstriction — have shown an association between enhanced airway constriction and enhanced radiohistamine flow across the airway mucosa in postallergic challenge situations as compared to control.<sup>5</sup> Similar experiments have not been performed in animal models of virus infection. In addition, the lack of specificity of pharmacologic agents as well as experimental limitations hinders the interpretation of data obtained from studies of human subjects with respect to this or other hypotheses. For example, lidocaine may not be a useful pharmacologic probe for these studies because it has effects not only on neural structures but, at a high concentration, also on smooth muscle and epithelial and mast cells.<sup>4, 12</sup> These findings make the utility of this agent as a specific blocker of afferent receptors questionable. Furthermore, the use of atropine to block vagal efferent activity does not allow one to choose between enhanced agonist flow to effector sites, increased sensitization of receptors, or alteration in receptor affinities as potential mechanisms for enhanced bronchoconstriction.

In summary, little is known about the specific mechanisms by which viruses induce transient airway activity in normal adults or subjects with pre-existing asthma. None of the above formulations adequately accounts for all the observations and available data; and conceivably other mechanisms may be involved. For example, changes in mast cells — e.g., recruitment of increased numbers of mast cells into airways, shifts in their distribution to submucosal to superficial areas, or increases in mast cell secretory rates possibly due to altered regulatory factors — may play a role in this abnormality. Further, the finding of cell-bound IgE during RSV infection in young children suggests other nonmast cell mechanisms of airway hyperreactivity during viral illnesses. Similarly, inflammatory mediators, complement

derived or others, may play a role in sensitizing elements that control bronchomotor tone.

### **Airway Sensitization**

Although viral disease clearly induces transient alterations in airway dynamics in both the normal and asthmatic, a more fundamental question that arises is whether infection predisposes to the development of specific allergy. Frick and co-workers<sup>1</sup> have specifically suggested that virus infections trigger the manifestations of atopy. They studied a group of children with strong family histories of atopy. They looked for the development of IgE antibody before, during, and after documented virus infection. They noted that upper respiratory infections occurred in most of these children one to two months prior to the onset of allergic sensitization. Although the normal incidence of viral infection in children may account for this association, this observation generates speculation as the role of infection in subsequent allergic sensitization.

As noted above, Richardson and colleagues demonstrated severe disruption of airway epithelium in a chicken model in response to an infection with an avian virus.<sup>32</sup> Using horseradish peroxidase (HRP) as a marker of protein permeability, they demonstrated an increased flow of HRP across airway surfaces after either virus infection or challenge with a chemical irritant (methacholine) as compared to control. Circulating anti-HRP titers over a 20-day interval were measured in all three groups. Enhanced anti-HRP production as compared to control was associated with the increased HRP entry induced by methacholine exposure. However, the relatively larger increase in rate of HRP entry into plasma associated with the virus infection was associated with depressed anti-HRP titers. Therefore, whereas a viral infection in this model appears to depress circulating antibody response to an exogenous antigen, the relevance of these observations to virus-induced development of allergy in human subjects remains unclear. Repeat studies in a mammalian species, measurements of homocytrophic antibody responses, and antibody responses over longer time intervals will be required to more fully explore this relationship.

### **SUMMARY**

The data reviewed demonstrate that viral and mycoplasma infections induce a spectrum of functional abnormalities in airways. Acute virus infections cause wheezing illnesses in both children and adults. Changes in peripheral airway function during infection with similar organisms are observed in other subjects, usually normal adults. The pathogenesis of these responses is unclear. Pathologic data do show that infection with these pathogens damages the airway epithelium. These changes appear to increase permeability of the respiratory epithelium to protein antigens and consequently may contribute to increased frequency of attacks in asthmatic subjects. In addition, increased mucosal permeability may enhance delivery of inhaled drugs to effector sites in airway walls to induce exaggerated bronchoconstrictor responses in clinical challenge situations. Whether



changes in the epithelium during infection, inducing greater antigen entry into the interstitium, results in subsequent development of specific allergy is not known and requires further study.

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