Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
THE ROLE OF RESPIRATORY VIRUSES IN ACUTE AND CHRONIC ASTHMA

Amjad Tuffaha, MD, James E. Gern, MD, and Robert F. Lemanske, Jr, MD

Respiratory tract infections caused by viruses, chlamydia, and mycoplasma have been implicated in the pathogenesis of asthma. Viruses have been demonstrated to be associated with asthma epidemiologically in at least two ways (Fig. 1). First, during infancy, certain viruses have been implicated as potentially being responsible for the inception of the asthmatic phenotype. Second, in patients, particularly children, with established asthma, viral upper respiratory tract infections play a significant role in producing acute exacerbations of airway obstruction that may result in frequent outpatient visits or hospitalizations. This article reviews these two areas by focusing first on mechanisms by which virus infections may lead to the development of asthma in infants and children and, second, on mechanisms by which virus infections may produce acute asthmatic symptoms in patients who already have established disease.

Supported by NIH Grants Al34891, HL56396, and 1RO1HL61879.

VIRAL INFECTIONS AND THE INCEPTION OF ASTHMA

Infections with respiratory syncytial virus (RSV) or parainfluenza virus (PIV) have received much attention because of their predestination to produce a pattern of symptoms termed bronchiolitis that parallels many of the features of childhood and adult asthma. Respiratory syncytial virus causes about 70% of these episodes and it is estimated that, by age 1 year, 50% to 65% of children will have been infected with this virus and 40% of these infections involve the lower respiratory tract. By age 2, nearly all children will have been infected with RSV at least once. Children aged 3 to 6 months are most prone to develop lower respiratory tract symptoms, suggesting that a developmental component (e.g., lung or immunologic maturation) may be involved as well.

The relationship between RSV infections during the first few years of life and the subsequent development of the asthmatic phenotype has been the subject of much interest as well as controversy. Variations in reporting...
Healthy infant

\[ \text{TUFFAHA et al} \]

Child or adult with asthma

\[ \text{Resolution} \quad \text{Asthma} \]

\[ \text{Wheezing Illness} \quad \text{Atopy} \]

\[ \text{Emergency room visits} \quad \text{Hospitalization} \]

**Figure 1.** Mechanisms by which viruses may influence either the inception of asthma or exacerbations of the underlying disease process once it has been established. RSV = respiratory syncytial virus; PIV = parainfluenza virus.

Longitudinal outcomes (e.g., recurrent wheezing, measurements of airway hyperresponsiveness, diagnosis of asthma) appear to be influenced mostly by the criteria used to define “bronchiolitis.” These criteria include the type of virus producing the symptoms (in addition to RSV, viruses that may contribute to the development of bronchiolitis in this age group could be PIV, coronavirus, influenza virus, and rhinovirus); the age at the time of infection; the nature and severity of symptoms required for inclusion; and, finally, the characteristics of both the study population (community versus hospital-based) and the study design (retrospective versus prospective). A number of long-term prospective studies of children admitted to a hospital with documented RSV-induced bronchiolitis have shown that about 75% experience wheezing in the first 2 years after the initial illness, more than 50% still wheeze 3 years later, and approximately 40% continue to wheeze after 5 years.42, 49, 73, 91, 117, 121

Additional insight into these areas recently was provided by the results of an 11-year prospective study involving 880 children who were enrolled at birth, followed for the development of lower respiratory tract illnesses (LRIs) in the first 3 years of life, and then evaluated for the presence or absence of physician-diagnosed asthma or a history of current wheezing at ages 6 and 11 years.14 Most importantly, lung function was evaluated in the first few months of life in a subset of these children prior to the development of a documented LRI. During the first 3 years of life, 7.4% had pneumonia documented radiographically and 44.7% had a significant LRI without pneumonia. Respiratory syncytial virus and PIV were identified in 36.4% and 7.3%, respectively, in the subjects with pneumonia, and in 35.6% and 15.2%, respectively, of the subjects with a LRI. At age 6, physician-diagnosed asthma was present in 13.6% (OR = 3.3), 10.2% (OR = 2.4), and 4.6% of the subjects with pneumonia, LRI, and no LRI, respectively. By age 11, these values increased to 25.9% (OR = 2.8), 16.1% (OR = 1.6), and 11%, respectively. Mean maximum volume at functional residual capacity values before any LRI were lower in children with pneumonia and with LRIs than in children with no LRIs. These values continued to be lower at age 6 and by age 11, when forced expiratory volume in 1 second (FEV\(_1\)) and FEF\(_{25-75}\) were recorded, similar group relationships persisted. Interestingly, despite the persistence of lowered baseline lung function in both the pneumonia and LRI groups, many of these deficits were markedly (but not completely) reduced following administration of albuterol.

In a second report, further follow-up of this large cohort of children demonstrated that the risk for both frequent (more than three episodes of wheezing per year) and infrequent (three episodes of wheezing per year) wheezing in relation to RSV lower respiratory illnesses decreased markedly with age and became nonsignificant by age 13.104 These data suggest that, although RSV infections contribute substantially to the expression of the asthmatic phenotype, other factors (e.g., genetic, environmental, developmental) ap-
pear to contribute as well, either in terms of its initial expression or the modification of the phenotype over time.

CONTRIBUTION OF ATOPY

In addition to premorbid lung function, the influence of atopy on the development of the asthmatic phenotype in relationship to viral infections has also been evaluated. Interactions between these two factors appear to be bidirectional and dynamic, in that the atopic state can influence the lower airway response to viral infections, and viral infections can influence the development of allergen sensitization, and interactions can occur when individuals are exposed simultaneously to both allergens and viruses.

Atopy can be defined as the genetic predisposition to the preferential development of an immunoglobulin (Ig)E antibody response to a variety of environmental allergens. As stated previously, atopy has been considered to be a risk factor for the development of childhood asthma and its influence on the pattern of responses following viral infections has been of interest to many investigative groups. It has also been suggested that atopy could be a significant predisposing factor for the development of acute bronchiolitis during RSV epidemics. Although some have found that children most likely to have persistent wheezing were those born to atopic parents, others have not.

Respiratory syncytial virus and the immune response

Respiratory syncytial virus infections may interact with immunoinflammatory mechanisms involved in immediate hypersensitivity responses in a number of ways. First, it has been suggested that viruses capable of infecting lower airway epithelium may lead to enhanced absorption of aeroallergens across the airway wall, predisposing to subsequent sensitization. Second, RSV-specific IgE antibody formation may lead to mast-cell–mediator release within the airway, resulting in the development of bronchospasm and the ingress of eosinophils. Third, airway resident and inflammatory cell generation of various cytokines (tumor necrosis factor [TNF], interleukin [IL]-1, IL-6, IL-8), chemokines (MIP-1α, RANTES, MCP-1), leukotrienes, and adhesion molecules (intercellular adhesion molecule) may further upregulate the ongoing inflammatory response. Finally, similar to various allergenic proteins, the processing of RSV antigens and their subsequent presentation to lymphocyte subpopulations may provide a unique mechanism of interaction to promote a T-helper 2 (Th2)-like response in a predisposed host.

Respiratory syncytial virus belongs to the family Paramyxoviridae, the genera Pneumovirus, and can be differentiated into two serologic subgroups, A and B. It has 10 genes, with 12 potential gene products. The G (attachment) and F (fusion) proteins are the major surface glycoproteins against which neutralizing antibody is directed.
have recently been expanded. Roman et al evaluated 15 hospitalized infants (1-15 months) with an acute lower respiratory tract infection caused by RSV. Compared with control infants, peripheral blood cells from infected children had suppressed IFN-γ production ex vivo and, although IL-4 production was also decreased, the IL-4/IFN-γ ratio was significantly increased. Renzi et al prospectively followed 26 infants hospitalized with bronchiolitis by obtaining blood samples at the time of illness and 5 months later, and found that immune responses during the acute infection correlated with long-term pulmonary outcomes. Blood lymphocytes, obtained during the time of bronchiolitis, produced less IFN-γ ex vivo in response to IL-2 and more IL-4 in response to D. farinae antigen in children who went on to develop a pattern of recurrent wheezing. Finally, lower IFN-γ production at the time of bronchiolitis has been demonstrated to be an indicator of reduced pulmonary function and increased responsiveness to histamine 5 months after bronchiolitis, and was related to the development of asthma after bronchiolitis in infants. In contrast, other groups have noted increased levels of IFN-γ respiratory tract secretions during RSV illnesses in infants and children with bronchiolitis and recurrent wheezing compared with those with upper respiratory tract symptoms only. Unfortunately, in all of the studies reported thus far, the pattern of cytokine response these infants had prior to infection was not evaluated, begging the question as to which of the observed results may be cause and which effect.

ANIMAL MODELS

To more comprehensively evaluate the relationships among virus infection, atopy (cytokine dysregulation of Th1/Th2 imbalance), and immune system or lung developmental components, a rat model of virus-induced airway dysfunction has been studied extensively. In this model, infection with PIV type 1 during a critical developmental time period (when the animals are weaning [3-4 weeks of age] as opposed to when they are neonates [4-5 days] or adults) produces chronic (8-12 weeks following infection), episodic, reversible airway inflammation and remodeling with associated alterations in airway physiology (increased resistance and methacholine responsiveness) that resemble human asthma in high (brown Norway strain) but not low (F344 strain) IgE antibody producing rats. The temporal progression of this asthma-like syndrome is associated with a Th1/Th2 imbalance within the lung, and its development can be significantly attenuated by the exogenous administration of IFN-γ just prior to and during the viral infection in the brown Norway responder strain. This model further supports the concept of both genetic (atopy; cytokine dysregulation or imbalance) and environmental factors (virus infection) being important in the inception of the asthmatic phenotype, as well as a developmental component contributing.

EFFECT OF VIRAL INFECTIONS IN PATIENTS WITH ASTHMA

Respiratory viruses are common causes of asthma exacerbations in asthmatic subjects of different age groups. Serology or culture detection methods of viruses initially indicated an association during asthma exacerbations despite the fact that these detection methods are relatively insensitive for viruses such as rhinovirus (RV). The use of reverse transcription polymerase chain reaction (RT-PCR) assays that are more sensitive for detection of RV have confirmed and expanded these initial observations. Indeed, Johnston et al found that 80% to 85% of school-aged children with acute wheezing episodes tested positive for a virus using RT-PCR and other standard virologic techniques. The virus most often detected was RV. Seasonal patterns of upper respiratory virus infections correlate closely with hospital admissions for asthma, particularly in pediatric age groups. These studies indicate that RV infections are the most common cause of asthma exacerbations in children, especially during spring and fall. Similar studies, performed in adults, found that about half of asthma exacerbations were associated with RV infection.

As discussed previously, in infancy, atopy may define a susceptibility of the host to
wheezing with respiratory infections. Duff et al.22 for example, studied children who presented to an emergency department with wheezing. Children over 2 years of age were more likely to have respiratory allergies or a confirmed respiratory viral infection compared with children with no wheezing. Children with the highest risk for wheezing were those who had respiratory allergies and respiratory viral infection, implying that respiratory viral infections and respiratory allergies may have synergistic effects on lower airway physiology and enhance the likelihood of wheezing with respiratory infection. In children less than 2 years of age, wheezing was also noted, but risk factors for wheezing were quite different. These infants were not allergic, had RSV as the major viral isolate, and had passive tobacco smoke exposure as a major risk factor for wheezing.

MECHANISMS OF VIRAL-INDUCED AIRWAY OBSTRUCTION AND ASTHMA

Development of Variable Airway Obstruction

Available epidemiologic data in children and adults have shown that episodic drops in peak flow measurements are associated with RV infections. This was found to correlate with an increase in asthma symptoms and nonspecific airway hyperresponsiveness following experimentally infecting asthmatic subjects with RV.41 Further studies by Grünberg et al.40 demonstrated that experimental RV16 infection leads to a transient drop in daily home recordings of FEV1 in subjects with asthma. This variable airway obstruction correlated significantly with cold symptoms, asthma symptoms, and the increase in airway hyperresponsiveness to histamine. Such daily variability in FEV1 reflects the inflammatory changes within the airway wall, which can be induced by the natural RV infection.

Increased Bronchial Hyperresponsiveness

Increased bronchial responsiveness has been found in normal and asthmatic subjects following infections with RV and influenza A.65, 66, 72 In a study by Cheung et al.15 14 subjects with mild asthma were inoculated with RV16 or placebo. The maximal contractile response to inhaled methacholine was significantly greater during the RV16 infection and remained elevated for up to 15 days after the acute infection. This study indicates that an upper respiratory viral infection can enhance the reactivity of the lower airway and the magnitude of bronchonstriction changes, which can persist for weeks after the acute infection.

Respiratory viral infections' effect on lower airway responses are also influenced by host factors. In particular, allergic subjects experience greater changes in airway responsiveness after viral infection than nonallergic control subjects.9, 34 Furthermore, subjects with lower FEV1 values tend to have greater changes in airway responsiveness during viral infection.34 These studies suggest that effects of pre-existing conditions such as allergy and intrinsic lower airway function on caliber are likely to contribute to airway hyperresponsiveness during respiratory viral infection.

Neural Control of the Airways

Potential mechanisms through which viral infections could potentially cause bronchoconstriction and increased airway responsiveness include enhancing parasympathetic bronchoconstrictive responses, stimulation of airway sensory nerves, and interference with the bronchodilatory functions of the nonadrenergic, noncholinergic neurons (Table 1). Because of difficulties in assessing dysfunction of pulmonary neural regulation in humans, most data that support these proposed mechanisms were derived in animal models of acute respiratory viral infection. Further definition of these pathways in humans will depend upon the development of new experimental techniques or inhibition of specific neural pathways.

Structural Effects on the Small Airways

Changes in small airways structure and function may also contribute significantly to
Table 1. NEURAL MECHANISMS IMPLICATED IN VIRUS-INDUCED AIRWAY DYSFUNCTION

| Effect of Virus                  | Potential Mechanisms                                         | References                                      |
|---------------------------------|--------------------------------------------------------------|-------------------------------------------------|
| Heightened parasympathetic      | • Increased efferent activity of efferent cholinergic nerves  | Buckner et al11                                 |
| responses                       | • Viral neuraminidase                                        | Fryer et al30, 31                               |
|                                 | • Eosinophil cationic protein-induced M2 dysfunction        | Jacoby et al82                                  |
|                                 | • M2-independent mechanisms                                  | Sorkness et al101                               |
|                                 | Enhanced contractile responses to neurokinins                | Jacoby et al83                                  |
|                                 | Reduced production of nitric oxide                           | Ladenius et al85                                |
| Bronchoconstriction secondary to |                                                                              |
| sensory C-fibers                |                                                                              |
| Inhibition of nonadrenergic-    |                                                                              |
| noncholinergic neurons          |                                                                              |

The severity of hyperinflation and gas exchange abnormalities noted in acute asthma exacerbations. The maximal airway contractile response to methacholine in mild asthmatic subjects is increased during a cold, which is probably secondary to excessive airway narrowing attributable to airway wall thickening, airway parenchymal uncoupling, or abnormalities in smooth muscle contraction.15 Significant changes in airway morphology are noticed in animals with acute viral respiratory illness that leads to marked bronchiolar narrowing and plugging. These changes include bronchiolar airway edema and cell infiltration, epithelial hyperplasia, and folding and sloughing of airway epithelial surfaces. In addition, rats with mild increases in pulmonary resistance and methacholine sensitivity during acute viral respiratory illness have evidence of air trapping and ventilation-perfusion mismatches.101 These latter findings indicate that viruses can induce significant changes in the peripheral airways that have significant functional outcomes in the absence of marked changes in measurements of airway obstruction and hyperresponsiveness.

**Effects of Respiratory Viruses on Airway Inflammation**

Respiratory viruses can cause inflammation and injury to healthy airways and can worsen injury in airways that are already inflamed, as demonstrable in asthma. Respiratory viruses can induce an inflammatory process by direct cytopathic effects on the airway epithelium (e.g., RSV bronchiolitis) and can induce an immune response to stop viral replication and eradicate the virus. The immune response to viral infection may be a double-edged sword, however, as virus-induced inflammation can also contribute to airway obstruction and respiratory symptoms. Indeed, although many common cold viruses (e.g., RV) do not produce significant cytopathic effects, possibly because few cells are infected, the immunoinflammatory response to the virus is probably the major cause of respiratory symptoms. In this section, the association between virus-induced immune responses and respiratory symptoms is explored.

**Role of Epithelial Cells**

Respiratory viruses replicate primarily in airway epithelial cells. In addition to serving as host cells, it is now well documented that epithelial cells also initiate the immune response to infections through the secretion of cytokines and chemokines. In vitro studies of epithelial cells or cell lines have demonstrated that respiratory viruses such as RV, RSV, and parainfluenzavirus can induce the secretion of many different proinflammatory cytokines (IL-1, TNF-α, GM-CSF, IL-6, IL-11) and chemokines (RANTES, IL-8, MIP-1α).10, 20, 23, 96, 98, 105 Epithelial-derived chemokines are likely to be an important signal in initiating antiviral responses through the recruitment of leukocytes to the airway. In support of this concept, IL-8, a potent neutrophil chemoattractant, is found in high levels in nasal secretions of children with virus-induced asthma, and levels of IL-8 correlate with the number of airway neutrophils and neutrophil myeloperoxidase levels (suggesting neutrophil activation).108 There is also evidence, however, that enhanced airway inflammation caused by chemokine secretion may also disturb normal air-
way physiology. Chemokine levels in nasal secretions correlate closely with cold symptoms, for example, and IL-8 levels correlate with virus-induced changes in airway responsiveness. Levels of epithelial-derived cytokines such as IL-6 and IL-11 also correlate with respiratory symptoms, and animal studies indicate that overexpression of IL-11 can cause bronchial hyperresponsiveness.

In addition to stimulating cytokine production, RV can upregulate epithelial cell surface expression of intercellular adhesion molecule-1, which, in addition to facilitating cell–cell adhesion, is the receptor for the major group of RV. This enhanced expression of adhesion proteins may contribute to the persistence and severity of inflammation in asthmatic subjects and, possibly, the greater susceptibility of asthmatic children to colds compared with nonasthmatic children.

Mechanisms for the activation of cytokine genes in epithelial cells and adhesion molecules are under investigation. It is known that nuclear factor-κ B activation is important in virus-induced transcriptional regulation of IL-6 and, possibly, for the synthesis of a variety of inflammatory cytokines. Nitric oxide may regulate virus-induced chemokine production through a posttranscriptional mechanism and by inhibiting viral replication; although a clinical study did not find a relationship between IL-8 and nitrate levels in nasal secretions.

Effect on Granulocytes

Granulocyte recruitment and activation seem to have an important role in the pathogenesis of virus-induced asthma exacerbations. Grünberg et al, for example, experimentally inoculated 35 atopic asthma subjects with either RV16 or placebo and found that neutrophil counts in the peripheral blood correlated with the cold and asthma symptom scores and cold-induced changes in airway hyperresponsiveness. In addition, eosinophil granular proteins and leukotriene C4 have been detected in the nasal secretions of infants and children with virus-induced wheezing illnesses. Increased concentrations of sputum eosinophil cationic protein found during the acute phase of RV infection correlated with increases in airway responsiveness in a group of adults with asthma after experimental inoculation with RV16. In vitro experiments indicate that RV does not activate eosinophils directly; it is more likely that inflammatory mediators and cytokines, secreted by virus-activated cells in the lung, contribute to eosinophil activation. Finally, guinea pigs infected with PIV develop airway eosinophils and airway hyperresponsiveness and this outcome is blocked if the guinea pigs are pretreated with IL-5–neutralizing antibody.

Role of Mononuclear Cells

Most respiratory viruses replicate quickly and, within a few days of inoculation, the quantity of viruses and viral proteins is sufficient to activate mononuclear cells in the airway. In vitro infection of human monocytes with respiratory viruses, for example, leads to a potent proinflammatory cytokine response by release of IL-8, IL-1, and TNF-α. Interleukin-1 and TNF-α can increase cell recruitment into the airway by enhancing adhesion molecule expression on endothelial cells. In addition, TNF-α has been associated with wheezing illnesses in infancy and the development of late-phase allergic reaction and asthma. Monocytes and macrophages also produce interferon (INF), and its appearance in nasal secretions coincides with the onset of the recovery process. In addition to cytokine production, macrophages incubated with RSV or PIV produce lipid mediators such as prostaglandin E2, platelet-activating factor, and thromboxane B2 that can augment airway inflammation.

Lymphocytes, including natural killer cells, CD8+ cytotoxic T cells, and CD4+ T cells, are involved in limiting viral replication and viral clearance. To test the possibility that variations in lymphocyte responses might account for variability in the ability to clear viral infections, Parry et al measured in vitro lymphocyte responses in a group of allergic subjects who were then inoculated with RV 16. Vigorous virus-induced responses (lymphocyte proliferation or IFN-γ secretion) before inoculation correlated with reduced viral shedding after inoculation. These results sug-
gest that factors related to the host cellular response help determine the degree of viral replication during respiratory viral infections. Further characterization of these host factors may lead to new therapeutic strategies for respiratory infections, a goal that is particularly important for people with asthma.

Several studies have shown that viral infections activate a wide range of T cells. Evidence for this comes from experiments in mice, in which most of the T cells found in the lung after an acute viral infection are not virus-specific, and in vitro studies, in which 25% to 50% of human peripheral blood T cells express the early activation marker CD69 after 24 hours in culture with RV. RANTES, induced by respiratory viruses, at high concentrations can also induce antigen-independent T-cell activation. These studies suggest that respiratory viruses can induce early, non-specific T-cell activation and recruitment that could significantly increase the intensity of airway inflammation, resulting in airway dysfunction and respiratory symptoms.

This hypothesis is supported by studies of volunteers infected with rhinovirus. Respiratory virus infections usually cause peripheral lymphopenia and increased numbers of lymphocytes in the upper and lower airways, for example. The degree of peripheral blood lymphopenia and lymphocytic infiltration of the airway epithelium has been correlated with the increases in airway responsiveness.

Interactions Between Viral Infections and Responses to Allergen

Although viral infections cause similar upper respiratory symptoms in allergic and non-allergic individuals, there is evidence of interactions between virus- and allergen-induced responses in the lower airway. Leman-ske and colleagues, for example, identified 10 patients with allergic rhinitis and experimentally infected them with RV16. The viral infection increased airway reactivity to both inhaled allergen and histamine, and also increased the frequency of a late allergic reaction to inhaled antigens. Moreover, Calhoun and colleagues used bronchoscopy to study the inflammatory response to allergen in individual lung segments before, during, and 1 month after RV16 infection. RV infection enhanced the immediate antigen-induced release of histamine, and also increased eosinophil recruitment of eosinophils to the lung.

SUMMARY

Respiratory infections can have dual effects related to asthma. First, there is increasing evidence that severe infections with RSV and PIV in infancy can alter lung development and physiology to increase the risks of subsequent wheezing and asthma. Second, infections with common cold viruses and influenza commonly precipitate wheezing symptoms in children and adults who already have established asthma, and RV appears to be the most important virus in producing exacerbations of the disease. The principal mechanisms by which this occurs appears to be viral replication in epithelial cells, triggering a cascade of inflammation involving granulocytes, macrophages, T cells, and secreted cytokines and mediators. The inflammatory process, although essential to clear the infection, augments pre-existing airway inflammation in asthma, leading to increased airway obstruction and lower respiratory tract symptoms. Greater understanding of virus-induced changes in inflammation and corresponding changes in airway physiology may lead to new therapeutic approaches to the treatment and prevention of virus-induced airway dysfunction.

References

1. Alwan WH, Kozlowska WJ, Openshaw PJM: Distinct types of lung disease caused by functional subsets of antiviral T cells. J Exp Med 179:81, 1994
2. Alwan WH, Record FM, Openshaw PJM: Phenotypic and functional characterization of T-cell lines specific for individual respiratory syncytial virus proteins. J Immunol 150:5211, 1993
3. Anticevich SZ, Hughes JM, Black JL, et al: Induction of human airway hyperresponsiveness by tumour necrosis factor-α. Eur J Pharmacol 284:221, 1995
4. Arnold R, König B, Galatti H, et al: Cytokine (IL-8, IL-6, TNF-α) and soluble TNF receptor-I release from human peripheral blood mononuclear cells after respiratory syncytial virus infection. Immunology 85:364, 1995
5. Bacon KB, Premack BA, Gardner P, et al: Activation
THE ROLE OF RESPIRATORY VIRUSES IN ACUTE AND CHRONIC ASTHMA

297

of dual T-cell signaling pathways by the chemokine RANTES. Science 269:1727, 1995

6. Balfour-Lynn IM, Valman HB, Wellings R, et al: Tumour necrosis factor-α and leukotriene-E4 production in wheezy infants. Clin Exp Allergy 24:121, 1994

7. Baraniuk JN, Lundgren JD, Mizoguchi H, et al: Bradykinin and respiratory mucous membranes. Analysis of bradykinin binding-site distribution and secretory responses in vitro and in vivo. Am Rev Respir Dis 141:706, 1990

8. Bardin PG, Fraenkel DJ, Sanderson G, et al: Amplified rhinovirus colds in atopic subjects. Clin Exp Allergy 24:457, 1994

9. Bardin PG, Sanderson G, Robinson BS, et al: Experimental rhinovirus infection in volunteers. Eur Respir J 9:2250, 1996

10. Becker S, Koren HS, Henke DC: Interleukin-8 expression in normal nasal epithelium and its modulation by infection with respiratory syncytial virus and cytokines tumor necrosis factor, interleukin-1 and interleukin-6. J Am Respir Cell Mol Biol 8:20, 1993

11. Beckner CK, Songsrude V, Dick EC, et al: In vivo and in vitro studies on the use of the guinea pig as a model for virus-provoked airway hyperreactivity. Am Rev Respir Dis 132:305, 1985

12. Calhoun WJ, Dick EC, Schwartz LB, et al: A common cold virus, rhinovirus 16, potentiates airway inflammation after segmental antigen broncho-provocation in allergic subjects. J Clin Invest 94:2200, 1994

13. Calhoun WJ, Dick EC, Schwartz LB, et al: A common cold virus, rhinovirus 16, potentiates airway inflammation after segmental antigen bronchoprovocation in allergic subjects. J Clin Invest 94:2200, 1994

14. Castro-Rodriguez JA, Holberg CJ, Wright AL, et al: Association of radiologically ascertained pneumonia before age 3 years with asthma-like symptoms and pulmonary function during childhood. A prospective study. Am J Respir Crit Care Med 159:1891, 1999

15. Cheung D, Dick EC, Timmers MC, et al: Rhinovirus infection causes long-lasting excessive airway narrowing in response to methacholine in asthmatic subjects in vivo. Am J Respir Crit Care Med 152:1490, 1995

16. Colasurdo GN, Hemming VG, Prince GA, et al: Human respiratory syncytial virus affects nonadrenergic noncholinergic inhibition in cotton rat airways. Am J Physiol 12:1396-13910, 1991

17. Comoy EE, Pestel J, Duez C, et al: The house-dust mite Dermatophagoides pteronyssinus, proinflammatory response after exposure to cockroach dust and house dust. J Immunol 125:1379, 1985

18. Cook PJ, Davies P, Tunnelliffe W, et al: Chlamydia pneumoniae and asthma. Thorax 53:254, 1998

19. Cunningham AF, Johnston SL, Julious SA, et al: Chronic Chlamydia pneumoniae infection and asthma exacerbations in children. Eur Respir J 11:345, 1998

20. DiCosmo BF, Geba GP, Picarella D, et al: Airway epithelial cell expression of interleukin-6 in transgenic mice. Uncoupling of airway inflammation and bronchial hyperreactivity. J Clin Invest 94:2028, 1994

21. Doherty PC, Hou S, Tripp RA: CD8+ T-cell memory in viruses. Curr Opin Immunol 6:545, 1994

22. Duff AL, Pomeranz ES, Gelber LE, et al: Risk factors for acute wheezing in infants and children: Viruses, passive smoke, and IgE antibodies to inhalant allergens. Pediatr 92:535, 1993

23. Einarsson O, Geba GP, Zhu Z, et al: Interleukin-11: Stimulation in vivo and in vitro by respiratory viruses and induction of airways hyperresponsiveness. J Clin Invest 4:915, 1996

24. Folkerts G, Busse WW, Nijkamp FP, et al: Virus-induced airway hyperresponsiveness and asthma. Am J Respir Crit Care Med 157:1708, 1998

25. Folkerts G, Esch BV, Jansen M, et al: Virus-induced airway hyperresponsiveness in guinea pigs in vivo: Study of broncho-alveolar cell number and activity. Eur J Pharmacol 228:219, 1992

26. Fraenkel DJ, Bardin PG, Sanderson G, et al: Lower airways inflammation during rhinovirus colds in normal and asthmatic subjects. Am J Respir Crit Care Med 151:879, 1995

27. Freihorst J, Piedra PA, Okamoto Y, et al: Effect of respiratory syncytial virus infection on the uptake of and immune response to other inhaled antigens. Proc Soc Exp Biol Med 188:191, 1988

28. Frick OL: Effect of respiratory and other virus infections on IgE immunoregulation. J Allergy Clin Immunol 78:1013, 1986

29. Frick OL, German DF, Mills J: Development of allergen in children. I. Association with virus infections. J Allergy Clin Immunol 63:228, 1979

30. Fryer AD, al Fakahany EE, Jacoby DB: Parainfluenza virus type 1 reduces the affinity of agonists for muscarinic receptors in guinea-pig lung and heart. Eur J Pharmacol 181:51, 1990

31. Fryer AD, Jacoby DB: Parainfluenza virus infection damages inhibitory M2 muscarinic receptors on pulmonary parasympathetic nerves in the guinea pig. Br J Pharmacol 102:267, 1991

32. Garafalo R, Kimpen JLL, Welliver RC, et al: Eosinophil degranulation in the respiratory tract during naturally acquired respiratory syncytial virus infection. J Pediatr 120:28, 1992

33. Gern JE, Busse WW: Role of T cells in virus-induced asthma. In Liggett SB, Meyers DA (eds): Genetics of Asthma. New York, Marcel Dekker, 1996, p 39

34. Gern JE, Calhoun W, Swenson C, et al: Rhinovirus infection preferentially increases lower airway responsiveness in allergic subjects. Am J Respir Crit Care Med 155:1872, 1997

35. Gern JE, Dick EC, Lee WM, et al: Rhinovirus enters but does not replicate inside monocytes and airway macrophages. J Immunol 156:621, 1996

36. Gern JE, Vrtis R, Kelly EAB, et al: Rhinovirus produces nonspecific activation of lymphocytes through a monocyte-dependent mechanism. J Immunol 157:1605, 1996

37. Gosset P, Tsicopoulos A, Wallaert B, et al: Increased secretion of tumor necrosis factor-α and interleukin-6 by alveolar macrophages consecutive to the development of the late asthmatic reaction. J Allergy Clin Immunol 88:561, 1991

38. Greve JM, Davis G, Meyer AM, et al: The major human rhinovirus receptor is ICAM-1. Cell 56:839, 1989

39. Grünberg K, Kuipers AP, de Klerk EPA, et al: Effects of experimental rhinovirus 16 infection on airway hyperresponsiveness to bradykinin in asthmatic subjects in vivo. Am J Respir Crit Care Med 155:833, 1997

40. Grünberg K, Timmers MC, de Klerk EPA, et al: Experimental rhinovirus 16 infection causes variable airway obstruction in subjects with atopic asthma. Am J Respir Crit Care Med 160:1375, 1999
Grüenberg K, Timmers MC, Smits HH, et al: Effect of experimental rhinovirus 16 colds on airway hyperresponsiveness to histamine and interleukin-8 in nasal lavage in asthmatic subjects in vivo. Clin Exp Allergy 27:36, 1997

Gurwitz D, Minderrot C, Levison H: Increased incidence of bronchial reactivity in children with a history of bronchiolitis. J Pediatr 98:251, 1981

Hahn DL, Dodge RW, Golubjatnikov R: Association of Chlamydia pneumoniae (strain TWAR) infection with wheezing, asthmatic bronchitis, and adult-onset asthma. JAMA 266:225, 1991

Hall CB: Respiratory syncytial virus: A continuing culprit and conundrum. J Pediatr 135:52-57, 1999

Handzel ZT, Busse WW, Sedgwick JB, et al: Eosinophil bind rhinovirus and activate virus-specific T cells. J Immunol 160:1279, 1998

Hansen G, Berry G, DeKruyff RH, et al: Allergen-specific Th1 cells fail to counterbalance Th2 cell-induced airway hyperactivity but cause severe airway inflammation. J Clin Invest 103:175, 1999

Harris AM, Bonville CA, Rosenberg HF, et al: Respiratory syncytial virus-induced chemokine expression in the lower airways. Eosinophil recruitment and degranulation. Am J Respir Crit Care Med 159:1918, 1999

Henricks PAJ, Van Esch B, Engels F, et al: Effects of parainfluenza type 3 virus on guinea pig pulmonary alveolar macrophage functions in vitro. Inflammation 17:663, 1993

Henry RL, Hodges IGC, Milner AD, et al: Respiratory problems 2 years after acute bronchiolitis in infancy. Arch Dis Child 58:713, 1983

Ichinose M, Barnes PJ: Bradykinin-induced airway microvascular leakage and bronchoconstriction are mediated via a bradykinin β1 receptor. Am Rev Respir Dis 142:1104, 1990

Jackson M, Scott R: Different patterns of cytokine induction in cultures of respiratory syncytial (RS) virus-specific human Th cell lines following stimulation with RS virus and RS virus proteins. J Med Virol 49:161, 1996

Jacoby DB, Gleich GJ, Fryer AD: Human eosinophil major basic protein is an endogenous allospecific antagonist at the inhibitory muscarinic M2 receptor. J Clin Invest 91:1314, 1993

Jacoby DB, Tamaoki J, Borson DB, et al: Influenza infection causes airway hyperresponsiveness by decreasing enkephalinase. J Appl Physiol 64:2653, 1988

Johnston SL, Papi A, Monick MM, et al: Rhinoviruses induce interleukin-8 mRNA and protein production in human monocytes. J Infect Dis 175:323, 1997

Johnston SL, Pattemore PK, Sanderson G, et al: The relationship between upper respiratory infections and hospital admissions for asthma: A time–trend analysis. Am J Respir Crit Care Med 154:654, 1996

Johnston SL, Pattemore PK, Sanderson G, et al: Role of virus infection in children with recurrent wheeze or cough [abstract]. Thorax Journal 48:1055-1055, 1993

Johnston SL, Pattemore PK, Sanderson G, et al: Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. BMJ 310:1225, 1995

Johnston SL, Xie P, Johnson W: Comparison of standard virology and PCR in diagnosis of rhinovirus and respiratory syncytial virus infections in nasal aspirates from children hospitalized with wheezing illness and bronchiolitis [abstract]. Am J Respir Crit Care Med 153:A503, 1996

Kaul P, Singh I, Turner RB: Effect of nitric oxide on rhinovirus replication and virus-induced interleukin-8 elaboration. Am J Respir Crit Care Med 159:1193, 1999

Kimpfen JLL, Garafalo R, Welliver RC, et al: Activation of human eosinophils in vitro by respiratory syncytial virus. Pediatr Res 32:160, 1992

Kraft M, Cassell GH, Herson JE, et al: Detection of Mycoplasma pneumoniae in the airways of adults with chronic asthma. Am J Respir Crit Care Med 158:998, 1998

Kumar A, Sorkness R, Kaplan MR, et al: Chronic, episodic, reversible airway obstruction after viral bronchiolitis in rats. Am J Respir Crit Care Med 155:130, 1997

Ladenius ARC, Folkerts G, Linde van der HJ, et al: Potentiation by viral respiratory infection of ovalbumin-induced guinea pig tracheal hyperresponsiveness: Role for tachykinins. Br J Pharmacol 115:1048, 1995

Ling I, Riedel F, Yap PL, et al: Atopy predisposing to acute bronchiolitis during an epidemic of respiratory syncytial virus. BMJ 284:1070, 1982

Laitinen LA, Elkin RB, Empey DW, et al: Bronchial hyperresponsiveness in normal subjects during attenuated influenza virus infection. Rev Respir Dis 143:358, 1991

Laitinen LA, Kava T: Bronchial reactivity following uncomplicated influenza A infection in healthy subjects and in asthmatic patients. Eur J Respir Dis 10:51, 1980

Landau LI: Bronchiolitis and asthma: Are they related? Thorax 49:293, 1994

Lemanske RF Jr, Dick EC, Swenson CA, et al: Rhinovirus upper respiratory infection increases airway hyperreactivity and late asthmatic reactions. J Clin Invest 83:1, 1989

Lemanske RF Jr, Dick EC, Swenson CA, et al: Rhinovirus upper respiratory infection increases airway hyperreactivity and late asthmatic reactions. J Clin Invest 83:1, 1989

Lemanske RF Jr, Lemen RJ, Gern JE: Infections in childhood. In Barnes PJ, Grunstein MM, Leff AR, et al (eds): Asthma. Philadelphia, Lippincott-Raven, 1997, p1207

Martinez FD, Wright AL, Taussig LM, et al: Asthma and wheezing in the first 6 years of life. N Engl J Med 332:133, 1995

Minor TE, Dick EC, Baker JW, et al: Rhinovirus and influenza type A infections as precipitants of asthma. Am Rev Respir Dis 112:149, 1976

Murray M, Webb MS, O’Callaghan C, et al: Respiratory status and allergy after bronchiolitis. Arch Dis Child 67:482, 1992

Nicholson KG, Kent JK, Ireland DC: Respiratory viruses and exacerbations of asthma in adults. BMJ 307:982, 1993

Noma T, Yoshizawa I: Induction of allergen-specific IL-2 responsiveness of lymphocytes after respiratory syncytial virus infection and prediction of onset of recurrent wheezing and bronchial asthma. J Allergy Clin Immunol 99:816, 1997

Olszewska-Pazdrak B, Casola A, Saito T, et al: Cell-specific expression of RANTES, MCP-1, and MIP-1α by lower airway epithelial cells and eosinophils infected with respiratory syncytial virus. J Virol 72:4756, 1998

Openshaw PJM: Immunopathological mechanisms in respiratory syncytial virus disease. Springer Seminars in Immunopathology 17:187, 1995
78. Panuska JR, Midulla F, Cirino NM, et al: Virus-induced alterations in macrophage production of tumor necrosis factor and prostaglandin-E2. Am J Physiol 259:L396-L402, 1990

79. Papi A, Johnston SL: Rhinovirus infection induces expression of its own receptor intercellular adhesion molecule 1 (ICAM-1) via increased NF-kappaB-mediated transcription. J Biol Chem 274:5707, 1999

80. Parry DE, Busse WW, Sukow KA, et al: Rhinovirus-induced peripheral blood mononuclear cell responses and outcome of experimental infection in allergic subjects. J Allergy Clin Immunol, in press

81. Patel JA, Kunimoto M, Sim TC, et al: Interleukin-1 alpha mediates the enhanced expression of intercellular adhesion molecule-1 in pulmonary epithelial cells infected with respiratory syncytial virus. Am J Respir Cell Mol Biol 13:602, 1995

82. Pattemore PK, Johnston SL, Bardin PG: Viruses as precipitants of asthma symptoms. I. Epidemiology. Clin Exp Allergy 22:325, 1992

83. Prescott SL, Macaubas C, Smallacombe T, et al: Development of allergen-specific T-cell memory in atopic and normal children. Lancet 350:946, 1997

84. Pullan CR, Hey EN: Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. BMJ 284:1665, 1982

85. Rabatic S, Gagro A, Lokar-Kolbas R, et al: Increase in nitric oxide production in bronchitis. J Allergy Clin Immunol 37:305, 1996

86. Rakes CP, Arruda E, Ingram JM, et al: Rhinovirus and respiratory syncytial virus in wheezing children requiring emergency care—ige and eosinophil analyses. Am J Respir Crit Care Med 159:785, 1999

87. Renzi PM, Turgeon JP, Marcotte JE, et al: Reduced interferon-gamma production in infants with bronchiolitis and asthma. Am J Respir Crit Care Med 159:1417, 1999

88. Renzi PM, Turgeon JP, Yang JP, et al: Cellular immunity is activated and a TH-2 response is associated with early wheezing in infants after bronchiolitis. J Pediatr 130:584, 1997

89. Roberts NJ: Different effects of influenza virus, respiratory syncytial virus, and sendai virus on human lymphocytes and macrophages. Infect Immun 35:1142, 1982

90. Roberts NJ, Prill AH, Mann TN: Interleukin-1 and interleukin-1 inhibitor production by human macrophages exposed to influenza virus or respiratory syncytial virus. J Exp Med 163:511, 1986

91. Rooney JC, Williams HE: The relationship between proved viral bronchitis and subsequent wheezing. J Pediatr 79:744, 1971

92. Ruuskanen O, Ogra PL: Respiratory syncytial virus. Curr Probl Pediatr 2:50, 1993

93. Saban R, Dick EC, Fishleder RL, et al: Enhancement by parainfluenza 3 infection of contractile responses to substance P and capsaicin in airway smooth muscle from the guinea pig. Am Rev Respir Dis 136:586, 1987

94. Sakamoto M, Ida S, Takishima T: Effect of influenza virus infection on allergic sensitization to aerosolized ovalbumin in mice. J Immunol 132:2614, 1984

95. Sanders SP, Siekierski ES, Porter JD, et al: Nitric oxide inhibits rhinovirus-induced cytokine production and viral replication in a human respiratory epithelial cell line. J Virol 72:934, 1998

96. Schroth MK, Grimm E, Frindt P, et al: Rhinovirus replication causes RANTES production in primary bronchial epithelial cells. Am J Respir Cell Mol Biol 20:1220, 1999

97. Seminario M-C, Squilace D, Bardin PG, et al: Increased levels of eosinophil major basic protein in nasal secretions in rhinovirus infection [abstract]. J Allergy Clin Immunol 95:259, 1995

98. Siddiqi A, Peeples M, Brees B, et al: Respiratory syncytial virus-induced release of RANTES and MIP-1 by bronchial epithelial and peripheral mononuclear cells. J Allergy Clin Immunol 37:305, 1996

99. Sigurs N, Bjarnason R, Sigurbergsson F, et al: Asthma and immunoglobulin-E antibodies after respiratory syncytial virus bronchiolitis: A prospective cohort study with matched controls. Pediatr 95:500, 1995

100. Skoner DP, Doyle WJ, Serokky J, et al: Lower airway responses to influenza A virus in healthy allergic and nonallergic subjects. Am J Respir Crit Care Med 154:661, 1996

101. Sorkness R, Clough JJ, Castleman WL, et al: Virus-induced airway obstruction and parasympathetic hyperresponsiveness in adult rats. Am J Respir Crit Care Med 150:28, 1994

102. Sorkness RL, Castleman WL, Kumar A, et al: Prevention of chronic post-bronchiolitis airway sequelae with interferon-gamma treatment in rats. Am J Respir Crit Care Med 160:705, 1999

103. Staunton DE, Merluzzi VJ, Rothlein R, et al: A cell adhesion molecule, ICAM-1, is the major surface receptor for rhinoviruses. Cell 56:849, 1989

104. Stein RT, Sherrill D, Morgan WJ, et al: Respiratory syncytial virus infection in early life and risk of wheeze and allergy by age 13 years. Lancet 354:541, 1999

105. Subauste MC, Jacoby DB, Richards S, et al: Infection of a human respiratory epithelial cell line with rhinovirus. Induction of cytokine release and modulation of susceptibility to infection by cytokine exposure. J Clin Invest 96:549, 1995

106. Takeuchi R, Tutsushi H, Osaki M, et al: Respiratory syncytial virus infection of neonatal monocytes stimulates synthesis of interferon regulatory factor-1 and interleukin-18 (IL-18)-converting enzyme and secretion of IL-18. J Virol 72:837, 1998

107. Tang W, Geba GP, Zheng T, et al: Targeted expression of IL-11 in the murine airway causes lymphocytic inflammation, bronchial remodelling, and airways obstruction. J Clin Invest 98:2845, 1996

108. Teran LM, Johnston SL, Schroder J-M, et al: Role of nasal interleukin-8 in neutrophil recruitment and activation in children with virus-induced asthma. Am J Respir Crit Care Med 155:1362, 1997

109. Tsutsuhi H, Matsuda K, Sone S, et al: Respiratory syncytial virus-induced cytokine production by neonatal macrophages. Clin Exp Immunol 106:442, 1996

110. Turner RB, Weingand KW, Yeh CH, et al: Association between interleukin-8 concentration in nasal secretions and severity of symptoms of experimental rhinovirus colds [see comments]. Clin Infect Dis 26:840, 1998

111. Uhl EW, Castleman WL, Sorkness RL, et al: Parainfluenza virus-induced persistence of airway inflammation, fibrosis, and dysfunction associated with TGF-beta expression in brown Norway rats. Am J Respir Crit Care Med 154:1834, 1996

112. Van Oosterhout AJM, Van Ark I, Folkerts G, et al: Antibody to interleukin-5 inhibits virus-induced airway hyperresponsiveness to histamine in guinea pigs. Am J Respir Crit Care Med 151:177, 1995
113. van Schaik SM, Tristram DA, Nagpal IS, et al: Increased production of IFN-γ and cysteinyl leukotrienes in virus-induced wheezing. J Allergy Clin Immunol 103:630, 1999

114. Villani A, Cirino NM, Baldi E, et al: Respiratory syncytial virus infection of human mononuclear phagocytes stimulates synthesis of platelet-activating factor. J Biol Chem 266:5472, 1991

115. Volvovitz B, Welliver RC, De Castro G, et al: The release of leukotrienes in the respiratory tract during infection with respiratory syncytial virus: Role in obstructive airway disease. Pediatr Res 24:504, 1988

116. Von Hertzen L, Töyrälä M, Gimishanov A, et al: Asthma, atopy and Chlamydia pneumoniae antibodies in adults. Clin Exp Allergy 29:522, 1999

117. Webb MSC, Henry RL, Milner AD, et al: Continuing respiratory problems three and a half years after acute viral bronchiolitis. Arch Dis Child 60:1064, 1985

118. Welliver RC: Immunologic mechanisms of virus-induced wheezing and asthma. J Pediatr 135:S14-S20, 1999

119. Welliver RC, Sun M, Rinaldo D, et al: Predictive value of respiratory syncytial virus-specific IgE responses for recurrent wheezing following bronchiolitis. J Pediatr 109:776, 1986

120. Welliver RC, Wong DT, Sun M, et al: The development of respiratory syncytial virus-specific IgE and the release of histamine in nasopharyngeal secretions after infection. N Engl J Med 305:841, 1981

121. Zweiman B, Schoenwetter WF, Pappano JE, et al: Patterns of allergic respiratory disease in children with a past history of bronchiolitis. J Allergy Clin Immunol 48:283, 1971

Address reprint requests to
Robert F. Lemanske, Jr, MD
Department of Pediatrics
University of Wisconsin
Children's Hospital
600 Highland Avenue H4/432
Madison, WI 53792