

American Thoracic Society Workshop

MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

Immunobiology of Asthma and Rhinitis Pathogenic Factors and Therapeutic Options

THIS EXECUTIVE SUMMARY WAS APPROVED BY THE ATS BOARD OF DIRECTORS, FEBRUARY 1999

Thomas B. Casale, M.D. (Nebraska Medical Research Institute, Papillion, NE): Asthma and rhinitis are two respiratory diseases commonly investigated, researched, and treated by American Thoracic Society members. These diseases are linked pathogenically, epidemiologically, and therapeutically. For example, a majority of patients with asthma have been reported to have nasal symptoms versus only a minority of the general population. The prevalence of asthma in patients with rhinitis is much higher than that reported in the general population. Pathophysiologic events critical to the development and clinical manifestations of these two diseases are similar. Indeed, many of the cells, mediators, cytokines, and neurotransmitters important in the biology of asthma and rhinitis are the same. Treatment of rhinitis has been shown to improve pulmonary function and decrease symptoms in patients with asthma. Furthermore, systemic therapies can treat both diseases concomitantly.

At a workshop titled "Immunobiology of Asthma and Rhinitis: Pathogenic Factors and Therapeutic Options," held in Montreal, Canada in June 1997, participants discussed commonalities and differences between asthma and rhinitis with regard to (1) pathogenesis (in the context of the structure and function of the upper and lower airways), including immune effector cells, mediators, neurogenic pathways, and immunobiology; (2) incidence, prevalence, and comorbidity of asthma and allergic rhinitis, examining each from the perspective of whether they are distinct entities, coincidental diseases, or interrelated conditions; and (3) treatment, with a focus on distinct therapies as well as current and future concomitant therapies. Specific sessions focused on four themes: (1) Immune Effector Cells and Mediators in the Pathogenesis of Asthma and Rhinitis; (2) Relationship between Neurogenic Pathways and Immunobiology of Asthma and Rhinitis; (3) Incidence, Prevalence, and Comorbidity of Asthma and Rhinitis; and (4) Current Therapies and Future Prospects for the Concomitant Treatment of Asthma and Rhinitis.

What follows is an Executive Summary of the Workshop Proceedings, which focuses on the four themes and concluding commentaries. The full text of the proceedings is available in print and on the World Wide Web through the American Thoracic Society at www.thoracic.org/statements/rhinitis/rhinitis.html.

Immune Effector Cells and Mediators in the Pathogenesis of Asthma and Rhinitis

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MA), Jeffrey M. Drazen, M.D. (Brigham and Women's Hospital, Boston, MA), Klaus F. Rabe, M.D. (Grosshansdorf Hospital, Grosshansdorf, Germany), Stephen P. Peters, M.D. (Jefferson Medical College, Philadelphia, PA), and Robert M. Naclerio, M.D. (University of Chicago, Chicago, IL): The consensus discussion focused primarily on models of allergic rhinitis and asthma because these conditions are better described with regard to provoking stimuli and pathogenesis. However, it was emphasized that nonallergic rhinitis, nasal polyposis, and sinusitis share many of the inflammatory features characteristic of asthma including stromal edema, increased mast cells and eosinophils, and epithelial abnormalities. In particular, nasal polyposis associated with nonallergic (intrinsic) asthma and aspirin intolerance provides an ideal model for examining eosinophilic airway inflammation and the role of leukotrienes.

The immune effector cells responsible for allergic reactions in both the lung and the nose include, most prominently, mast cells (1), T lymphocytes (2), and eosinophils (2-5). After sensitization of a susceptible individual and the synthesis and binding of allergen-specific IgE to target cells, allergen exposure results in a characteristic series of events orchestrated by these cells. What is remarkable about the preformed and newly synthesized mediators (e.g., histamine, prostaglandins, leukotrienes, proteases, hydrolases, and cytotoxic proteins) and cytokines/chemokines produced by these cells is both their variety and their redundancy across different cellular elements. This is especially true for the cytokines/chemokines important for eosinophil development, recruitment, and activation, that is, interleukin 3 (IL-3), IL-4, IL-5, IL-13, granulocyte-macrophage colony-stimulating factor (GM-CSF), eotaxin, and RANTES (regulation on activation, normal T cell expressed and secreted).

The basic aspects of the machinery needed to produce an IgE-mediated inflammatory response in the lung appear to be the same in allergic subjects with and without asthma. For example, 24 h after segmental ragweed challenge, the pulmonary inflammatory response was the same in a group of 19 ragweed-allergic subjects with rhinitis as it was in a group of 27 ragweed-allergic subjects with asthma and rhinitis, as measured by the quantities of total cells, macrophages/monocytes, eosinophils, lymphocytes, neutrophils, total protein, and eosinophil cationic protein in bronchoalveolar lavage (BAL) fluid (6). However, factors responsible for determining whether an individual has allergic rhinitis alone rather than rhinitis and asthma are poorly understood.

CD4⁺ T cells play an essential role in allergic rhinitis and asthma, both as part of the sensitization phase to antigen, providing help to B cells for IgE synthesis, and as part of the inflammatory cascade during the subsequent symptomatic phases of antigen exposure (7). The factors responsible for the accumu-

lation of CD4⁺ T cells in allergic respiratory diseases are many and interact in complex networks to yield the inflammatory reactions seen in allergic rhinitis and asthma. Several studies (8–11) support the importance of IL-16 in the accumulation of CD4⁺ T cells in both the upper and lower airways.

Mast cell accumulation in the airways, an event mediated in part through the release of cytokines by CD4⁺ T cells, is an important pathophysiologic event in both allergic rhinitis and asthma. The specific biochemical events resulting from mast cell degranulation are similar in the upper and lower airways, but the physiologic consequences differ owing to the target organs affected. Although mucosal edema mediated by mast cell degranulation contributes to both upper and lower airway obstruction, the prominence of smooth muscle contraction in the lower airways distinguishes the immediate allergic response in the lower airways from that in the upper airways. Indeed, since histamine is not a potent bronchoconstricting agent, its role in rhinitis and asthma is significantly different. Consequently, the beneficial effects of antihistamines in allergic rhinitis are much greater than those in allergic asthma.

Subsequent to the immediate response to antigen-induced mast cell degranulation, there is often a later response. In both the upper and lower airways, this late response is manifested physiologically by airway obstruction. However, basophils play a potentially important role in the late response in the nose, but not in the lung (12, 13). Nonetheless, the late response in both the upper and lower airways is also manifested by an influx of inflammatory cells, especially eosinophils, into the airways, and increased airway reactivity.

Eosinophil infiltration in allergic rhinitis and asthma may arise from the release of a variety of mediators and cytokines from mast cells, T lymphocytes, epithelial cells, and in the lower airways, smooth muscle cells. The tissue damage observed in both allergic rhinitis and asthma may in part be mediated by eosinophils. The range of eosinophil products, both protein and lipid, that could contribute to the pathophysiology of airway diseases is extensive (14, 15).

The importance of leukotrienes as both chemoattractants for eosinophils and mediators produced by eosinophils was stressed. Leukotrienes have a variety of important biologic actions that contribute to the pathophysiology of asthma and rhinitis, including the ability to produce or increase smooth muscle contraction, mucous secretion, vascular permeability, and cellular infiltration. 5-Lipoxygenase (5-LO) is a critical enzyme in the production of leukotrienes. It has been shown that pharmacological inhibition of the action of 5-LO or antagonism of the action of the cysteinyl leukotrienes at their receptor (cysteinyl LT₁) is associated with an amelioration of asthma and rhinitis. In these trials, there was substantial variability in response among the subjects studied. However, there is reason to believe that an understanding of the factors regulating 5-LO enzyme activity will provide insight into the pathological processes that arise from leukotriene excess.

There is a family of mutations in the 5-LO promoter region that appear to modify 5-LO expression. If the genotype at the 5-LO promoter locus relates to the clinical response to treatment, then this suggests that it will be possible to predict which individuals will have salutary response to clinical treatment with a leukotriene receptor antagonist or synthesis inhibitor. If responsiveness is genetically determined, we would also predict an effect with respect to both upper and lower airway disease. This point has yet to be established.

The mechanism of activation of eosinophils was believed to be as poorly understood in the lower airways as in the upper airways. It is likely that the mechanism of priming is the same, and is directly related to molecular adhesion. Actual linkage

with specific adhesion molecules has been found to upregulate the secretory process of eosinophils to many stimuli. Thus, a series of cytokines, mediators, matrix interactions, and a priming sequence was outlined and thought to be similar for both the upper and lower airways. The “priming” sequence is the result of inflammatory cells binding to either endothelium or matrix protein through specific adhesion matrixes, leading to inflammatory events such as secretion of leukotrienes.

Eosinophils may also be involved in airway remodeling, which can lead to refractory asthma. However, it is difficult to define exactly what constitutes airway remodeling and whether the process is physiological, pharmacological, or anatomical. Subendothelial fibrosis is seen in the remodeling process in allergic asthma, but there is no analogous process in allergic rhinitis. This suggests a difference in end-organ responses in diseases that share common pathophysiologic mechanisms.

Other factors that might contribute to differences in pulmonary versus nasal responses include differences in airway geometry, surface area blood supplies, and exposure to environmental triggers. Additional potentially important differences include the residence time of inflammatory cells, mediators, and cytokines in the lung versus the nose, and the kinetics and mechanism of repair of epithelium after an inflammatory event. There might be both a prolonged residence time of inflammatory cells and repair time for damaged epithelium in the lung versus nose after antigen challenge (16).

Differences in the upper and lower airway epithelium with regard to rhinitis and asthma include the degree to which epithelium is shedding and a greater degree of epithelial heterogeneity in the lung, factors that could influence the duration of inflammation in the nose versus the lung. Epithelial shedding, which during asthma occurs to a variable degree at different times and locations in the conducting airways of the lung, does not occur to the same degree in the nose. The epithelium produces substances involved in the bronchoconstrictor response including lipid mediators, endothelin and cytokines; thus sloughing could in some way terminate or ameliorate that response. There is no analog of this process in the nose or sinuses. Greater heterogeneity in the epithelium of the lower rather than the upper airways might exist, reflected in duration of inflammation as well.

Another important difference between rhinitis and asthma is the role of smooth muscle. Airway smooth muscle cells have been found to be secretory cells, and thus part of the autocrine process. Because there is little smooth muscle in the nose this represents a substantial difference between allergic rhinitis and allergic asthma. Airway smooth muscle can produce RANTES (17), eotaxin, and GM-CSF and, as has been shown in a number of laboratories, prostaglandin E₂ (PGE₂), which can act either as a bronchodilator or bronchoconstrictor. Evidence indicates that adhesion molecules on smooth muscle have counterligands corresponding to those on inflammatory cells. However, the precise role of these adhesion molecules in upregulating the constrictor response or in bringing inflammatory cells nearer the airway smooth muscle is not yet understood physiologically.

Finally, the nose and lung differ in both their degree of exposure to environmental insults such as allergens and irritants, and the degree and mechanisms by which effector molecules such as histamine and leukotrienes produce pathologic effects in the nose versus the lung.

Thus, there are many similarities, but also some significant differences in the types and role of immune effector cells and mediators in the pathogenesis of rhinitis and asthma. Workshop participants emphasized that there was much to be learned yet, and they identified some key questions for future research, including the following:

1. Is the initiating sequence for atopy, allergic rhinitis, and allergic asthma the same, or different? Also, are there differences in the pathogenic cascade in chronic allergic versus nonallergic rhinitis and asthma?
2. What is the precise relationship between airway inflammation and the clinical manifestations of rhinitis and asthma?
3. What are the key inflammatory mechanisms in common for rhinitis and asthma that could be targeted for concomitant therapeutic modalities?

Relationship between Neurogenic Pathways and Immunobiology of Asthma and Rhinitis

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One of the mechanisms postulated for rhinitis-associated asthma is a common neurogenic pathway with upper airway stimulation directly leading to reflex-mediated bronchoconstriction. A subpopulation of patients with asthma have active nasobronchial and sinobronchial reflexes that produce an ~10 to 12% fall in FEV₁. Cold air nasal provocation can also activate a reflex decrease in FEV₁. Conversely, histamine bronchial provocation can increase nasal airflow resistance, suggesting modulation of central reflexes affecting both organs. Viral infections may affect both upper and lower airways, leading to the common association of rhinitis followed by an asthma exacerbation. Production of IL-11 during rhinovirus infections may promote neural and other mechanisms of airway inflammation (18).

Nerves containing the tachykinins neurokinin A and substance P, vasoactive intestinal peptide (VIP), and other neurotransmitters innervate upper airway submucosal glands, vessels, myoepithelium, and epithelium (19). In sensitized animals or humans, the application of allergen to the nasal mucosa can result not only in the immediate- and late-phase response, but also in neuropeptide release. It is postulated that these peptides alter secretion, airway smooth muscle tone, vasodilation, and possibly cellular recruitment, leading to changes in nasal airway conductance. Similar events are postulated to occur in the lower airways, contributing to the pathogenesis of asthma.

In the upper and central airways, inflammation-induced regulation of neuronal function is most obviously evidenced by conscious reflexes such as coughing and sneezing. In peripheral airways, immunologic alteration of neuronal activity occurs at a subconscious level, and consequently receives relatively little attention from those interested in the pathogenesis of airway disease. Yet, the innervation of the small airways serves to regulate the function of cells relevant to asthma, including smooth muscle, glandular, vasculature, and interstitial cells.

Anatomical, pharmacological, and physiological studies support the hypothesis that virtually all aspects of airway inflammation may be influenced by autonomic and/or afferent neurons. The participation of afferent nerve fibers in inflammation may occur as a result of axon reflexes, whereby action potentials travel not only centrally, but also back down collateral

branches of the axon to evoke neuropeptide release into the airway wall (20, 21). Released afferent or efferent neurotransmitters may then interact with receptors on nearby airway cells to influence their function. Both rhinitis and asthma are associated with airway hyperresponsiveness, and this physiologic feature is due to an interaction of the neurogenic and inflammatory pathways.

As indicated previously, mast cells are important in the pathogenesis of allergic rhinitis and asthma. There is evidence indicating a preferential growth of neurites toward mast cells (22). Furthermore, inflammatory mediators released from mast cells and other inflammatory cells, including bradykinin, PGE₂ and leukotriene D₄ (LTD₄), all appear capable of enhancing the release of tachykinins (23). In addition, neurotrophins, such as nerve growth factor (NGF), and IL-6 and IL-11, also increase nociceptive nerve activity, and may have potent effects on airway inflammation induced by allergic, viral, irritant, and pollutant stimuli (24). Other cytokines such as IL-1 β and IL-8 can depolarize sensory nerves.

Proinflammatory cytokines such as IL-1 can be induced by substance P in epithelial cells and macrophages, setting the stage for a circuit involving nerves and inflammatory pathways. Indeed, epithelial cells can synthesize both proinflammatory cytokines as well as neurotrophic factors, thus further potentiating and enhancing the outgrowth of nerves, neuropeptide formation and release, and inflammation in response to activation of the epithelium. The role of NGF, in particular, as both a mast cell and neuronal differentiation factor, highlights the intricate connections of these two systems within mucosal tissues. The effects of NGF in conjunction with the other hematopoietic cytokines on stimulation of the growth and differentiation of eosinophils and basophils (25), the characteristic cells of the late-phase allergic inflammatory response in the airway, suggest that NGF may also play an important role in the recruitment and differentiation of these cells in a variety of airway diseases such as asthma, allergic and nonallergic rhinitis, sinusitis, and nasal polyposis. Over the years, studies have also emphasized a role for hematopoietic pathways, and NGF, in synergy with either GM-CSF or IL-5, in the elicitation of eosinophil and basophil progenitors from the bone marrow through the blood and into the airway tissues (25).

Thus, there are many similarities in the neurogenic pathways and their effects, including their interactions with key inflammatory and structural cells, in the upper and lower airways.

Neurogenically mediated inflammation is regulated by enzymes that break down many of the neuropeptides. The most important enzymes in controlling the inflammatory response are neutral endopeptidase (NEP) (26) and angiotensin-converting enzyme (ACE). Inhibiting these enzymes markedly potentiates the inflammatory response to both endogenous and exogenous tachykinins. Furthermore, levels of these enzymes are decreased by viral infections (27), and by exposure to cigarette smoke and oxidants (28), suggesting that the potentiation of neurogenic inflammation may contribute to exacerbations of airway disease caused by these stimuli. Conversely, the activity of these enzymes is increased *in vivo* after treatment with dexamethasone, and this decreases neurogenic inflammatory responses in the airways (29).

Differences in the function of neurotransmitters in the upper and lower airways are also apparent, and as with inflammatory pathways, depend in part on dissimilarities in the upper and lower airway anatomy. For example, in the lower airways, neurokinin A mediates bronchoconstriction through NK₂ receptors on smooth muscle. However, its effects on upper airway functions contributing to rhinitis are less clear owing to the lack of airway smooth muscle in nasal tissue.

Indeed, vasodilation mediated by sensory and parasympathetic nerves is the most important factor contributing to nasal airflow resistance. However, in the lower airways, bronchoconstriction mediated by tachykinins, and to a greater extent parasympathetic mechanisms, is one of the most important factors in regulating lower airflow resistance.

The importance of parasympathetic and muscarinic receptor subtypes in asthma was stressed. No analogous roles for these receptors in rhinitis have been found. The parasympathetic nerves release acetylcholine, which binds to M₃ muscarinic receptors, causing contraction of the muscle and airway narrowing. The release of acetylcholine is also controlled by an inhibitory M₂ muscarinic neural receptor, thus creating a negative feedback mechanism for the control of acetylcholine release. The bronchoprotective effects of M₂ muscarinic receptors may be dysfunctional in asthma. M₂ receptors have been found to be dysfunctional after exposure to ozone, parainfluenza viruses, and antigen (30–35). Eosinophils, through major basic protein, have also been found to produce dysfunction of M₂ receptors (36, 37).

Thus, although there are many similarities, some substantial differences also exist in the roles of neurogenic pathways and neurotransmitters in the pathogenesis of asthma and rhinitis (38, 39). The interactions between these neurotransmitters and inflammatory cells are important factors in the immunobiology of asthma and rhinitis. However, much is yet to be learned, and several key areas were identified for future research, including the following:

1. What are the exact effects of neuropeptides on the recruitment and function of inflammatory cells in the nasal and bronchial mucosa?
2. What are the key neurogenic mechanisms that could be targeted for distinct, and perhaps concomitant, therapies for rhinitis and asthma?

Incidence, Prevalence, and Comorbidity of Asthma and Rhinitis

Scott T. Weiss, M.D., M.S. (Brigham and Women's Hospital, Boston, MA), John W. Georgitis, M.D. (Bowman Gray School of Medicine, Winston-Salem, NC), Fernando Martinez, M.D. (University of Arizona, Tucson, AZ), Robert Lemanske, M.D. (University of Wisconsin Hospital, Madison, WI), and Anne L. Wright, Ph.D. (University of Arizona, Tucson, AZ): There have been significant changes in the epidemiology of asthma. Prevalence, particularly in children under the age of 6 yr, seems to be increasing; hospitalizations and emergency unit visits are also increasing. From 1982 to 1992, the overall age-adjusted prevalence rate for self-reported asthma in the United States increased by 42%. Among 5- to 34-yr-olds with a diagnosis of asthma, for whom prevalence rates are thought to be most accurate, the rate increased 52%. The largest increase appears to be in persons under 18 yr of age (40). These statistics are complicated because there is no "gold standard" for the diagnosis of asthma. Thus, epidemiologists have relied on patient self-reports of doctor diagnoses to determine incidence and prevalence rates. Airway hyperresponsiveness with wheezing has been proposed as the definition for epidemiological purposes. Because asthma affects approximately 18 million Americans, the costs of asthma care are enormous, estimated at approximately \$6 billion annually (41). Three issues that may help explain the increased prevalence of asthma and morbidity are changes in risk factors, access to medical care, and treatment.

The increase in hospitalizations for asthma is most pronounced in children up to age 4 yr, where the rate per 1,000 in-

creased from 3.2 to 5.5 between 1979 and 1990. The rate of increase for all children under 17 yr, 1.6 to 2.8 per 1,000, was slightly less (40). Overall, asthma mortality in the United States is low, although there has been a slight increase in the past 10 yr (42).

Asthma mortality in urban, mostly minority, populations approximates the highest asthma mortality rates anywhere in the world, suggesting that access to health care, and in particular, access to highly effective inhaled antiinflammatory medications, may be contributing to the increased prevalence and morbidity of asthma in the United States. Changes in risk factors may also play a role. For example, maternal cigarette smoking is associated with the development of asthma in early childhood, and cigarette smoking has increased among women of childbearing age, particularly the poor. However, the changes in maternal smoking rates are not sufficient to account for the increase in asthma prevalence and morbidity. The role of indoor allergens as causal factors in childhood asthma is still being studied. House dust mites, fungi (*Alternaria*), cockroaches, cats, and dogs are all important sources of allergens, although it seems unlikely that allergens alone are contributing to the increase in asthma. Premature birth is a risk factor for the development of asthma, and modern approaches have improved the survival of infants as small as 1,000 g. However, the absolute numbers of these infants are small, and thus probably do not contribute in any substantial way to the increase in asthma prevalence.

Theories regarding the potential role of infections in the pathogenesis of asthma were reviewed. Some viruses, especially respiratory syncytial virus, can induce atopy and IgE in genetically susceptible individuals. Certain respiratory infections, such as measles and bacterial infections, may predispose airway lymphocytes to a helper T cell type 1 (Th1) phenotype. This is in contrast to the Th2 phenotype seen typically in asthma, and is characterized by the production of interleukins 4 and 5. Shirakawa and coworkers (43) reported that in 6- and 12-yr-olds, those who became tuberculin positive either by or after the age of 6 yr had a dramatically lower prevalence of atopy and of asthma at the age of 12 yr than subjects who did not. This phenotypic pattern may have been due to a genetically determined exuberant Th1 response, or to an environmental tuberculin exposure that resulted in a preferential Th1 response. If true, the number and severity of viral and bacterial respiratory infections and their timing in early childhood may be critical in the differentiation of helper T phenotypes, and hence the development of asthma. These respiratory infections may actually protect against the development of a Th2 phenotype. This is a hypothesis that is clearly in need of further testing.

The incidence, prevalence, and morbidity of chronic rhinitis were reviewed. Rhinitis ranks high as a common disorder, and affects individuals during their most productive years of childhood and young adulthood (44). Chronic rhinitis is associated with asthma, sinusitis, nasal polyps, and chronic otitis. It is an expensive disorder to manage, with high indirect costs. The true incidence of allergic rhinitis is highly variable, yet this entity is known to occur more often in atopic than in non-atopic families (45).

An estimated 5 to 40% of the general population suffers from rhinitis. Furthermore, 5 to 22% of asymptomatic individuals have positive skin tests (46), and many of these individuals may develop allergic rhinitis over time. There is a close relationship between skin test positivity and reported symptoms of nasal allergy (47).

Treatment costs for chronic rhinitis are variable; the best estimate is \$2.4 billion annually in the United States (48). In 1994, 9 million prescriptions were written for nasal corticoste-

roids; worldwide, antihistamines accounted for more than 1 billion prescriptions (49). Between 20 and 80% of patients are noncompliant with their medications (48).

Allergic rhinitis clearly affects activities of daily living, including nasal and nonnasal symptoms, emotional function, sleep, and overall quality of life (50, 51). Adolescent patients with chronic rhinitis tend to have psychological problems. In addition, there is an association with depression, fearfulness, and fatigue. Mood and cognitive impairments have been associated with chronic rhinitis.

It was stressed that asthma develops more commonly in patients with chronic rhinitis, especially seasonal allergic rhinitis. The Tucson Children's Respiratory Study examined the association between allergic rhinitis in childhood and asthma (52). Parents completed questionnaires regarding respiratory symptoms and risk factors for asthma for their children at a mean age of 1.6, 2.9, and 6.2 yr. Hazard ratios calculated for incidence of asthma revealed that onset of physician-diagnosed allergic rhinitis in infancy was associated with twice the odds of developing asthma by age 11 yr, even after adjusting for other risk factors. Thus, physician-diagnosed allergic rhinitis in the first year of life is a significant risk factor for asthma by age 11 yr, independent of other established risk factors, and future research should focus on this association.

Rhinitis and asthma may share common etiologic pathways, but these conditions are ultimately expressed differently. Moreover, each condition may itself reach heterogeneous end points, resulting in an array of clinical presentations and therapeutic responses. The risk factors for the two conditions also differ, making the formulation of a common central definition even more difficult.

Three core features that characterize the most prevalent form of asthma are early onset, allergic sensitization, and persistent and severe symptoms when left untreated. The prevalence of asthma associated with allergic sensitization appears to be greater than previously believed. Most of the epidemiological data on which the prevalence of asthma (5%) is based are derived from the late 1970s and early 1980s. In the United States, however, there are few studies of cumulative incidence of asthma during childhood that continue to the ages of adolescence and early adulthood.

The ongoing epidemiological study in Tucson suggests that by age 11 yr, 22.6% of all children have received a diagnosis of asthma from a physician at least once. Of these, 72.2% have active asthma at age 11 yr. The Tucson study also suggests that the association between active asthma and allergic rhinitis is seen not only cross-sectionally, but also longitudinally. Comparisons between transient wheezers (who wheeze during the first year of life and then stop), and persistent wheezers (who have symptoms and wheezing that persist) suggest that there may be a congenital inherited phenomenon associated with a "lung factor" that makes subjects with asthma different from subjects with rhinitis. However, there is likely also an "acquired factor," which may be associated with an altered growth of the lung and a subsequent decrease in lung function. A longitudinal epidemiologic study from Rochester, Minnesota (53) has found that in those 30, 40, or 50 yr of age who have symptoms of asthma, these symptoms can be traced to their first year of life.

A frequently asked question, "Does rhinitis cause asthma?" was addressed. Some data have indicated that the early development of rhinitis and symptoms of asthma is associated with a common risk factor for both: decreased production of interferon- γ by peripheral blood mononuclear cells. However, because only a small proportion of those who develop allergic rhinitis will also develop asthma, investigators have speculated

that a specific alteration in the immune system occurs preferentially, or differentially, in the lungs that permits a deviation from this initial common pathway. Additional alterations that occur early in life may be related to environmental factors. These may be either positive influences, such as early exposure to allergens, or negative influences that are absent, such as certain viral or mycobacterial infections. Additional data indicate that a genetic predisposition to bronchial hyperresponsiveness and some characteristic of the lung, altered by the environment with respect to immune reactivity, produce asthma (43).

Hypotheses regarding genetic predisposition are supported by multivariate analyses. Hazard ratios demonstrate that maternal and paternal physician-diagnosed asthma remain strong independent risk factors for the development of asthma. Ongoing studies have determined that asthma is a polygenic disease, with genetic predisposition more important in some population groups than others. Ultimately, understanding the human genome will elucidate mechanisms of asthma, but this understanding is not likely to explain the disease in its entirety.

It was concluded that the association that is seen between allergic rhinitis and asthma is most likely due to a common alteration of an immune system pathway. Epidemiologic data suggest that this consists of a relative imbalance between Th1-like and Th2-like cytokine responses in these subjects. The individual's pattern of response appears to exist before the development of allergic rhinitis and asthma. However, in order to develop asthma, an additional "lung factor" appears to be necessary. This factor appears to be multifaceted and reflects a genetic determination of bronchial hyperresponsiveness and an interaction between an altered immune system and a specific form of lung development that occurs in subjects who are exposed (or not) to certain factors present in the environment.

Important questions to direct research in this area include the following:

1. What is the relationship between childhood viral or bacterial infections and the subsequent development of asthma and/or allergic rhinitis?
2. What is the relative importance of genetic versus environmental factors?

Current Therapies and Future Prospects for the Concomitant Treatment of Asthma and Rhinitis

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The rationale for a number of "nonspecific" (e.g., theophylline and corticosteroids) and specific (e.g., antileukotrienes) approaches to asthma therapy was discussed.

Theophylline is a weak, rapid-acting bronchodilator, whose mechanism of action may involve inhibition of phosphodiesterases, activation of adenosine receptors, or, as suggested more recently, an antiinflammatory effect (54). Theophylline may also have an effect on the lipoxygenase pathway and decrease LTB₄ production by macrophages. These effects appear to correlate with improvement in nocturnal asthma physiology.

Inhaled corticosteroids have become the "gold standard" for the treatment of asthma, although much remains unknown

regarding the mechanisms behind their antiinflammatory effects. Although corticosteroids are more effective at improving FEV₁ and peak flow than bronchial reactivity, their antiinflammatory effects correlate better and more consistently with methacholine reactivity than they do with FEV₁. Glucocorticoids bind to both positive and negative glucocorticoid response elements in the nucleus, and to transcription factors such as nuclear factor $\kappa\beta$ (NF- $\kappa\beta$) and activating protein 1 (AP-1). The effect of glucocorticoids on cellular migration is believed to involve regulation of cytokine production through these mechanisms (55). Glucocorticoids also increase the apoptosis of eosinophils and lead to a decrease in the half-life of eosinophils in tissue. Effects of glucocorticoids on lipid mediators are much less clear.

The cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄) are potent bronchoconstrictors, modulators of production and clearance of mucus, and inducers of edema formation. Leukotriene B₄ is a potent neutrophil and eosinophil chemoattractant and activator. Leukotriene receptor antagonists (LTRAs) have a direct effect on the actions of the cysteinyl LTs, while 5-LO inhibitors prevent the formation of LTB₄ and the cysteinyl LTs. The LT-modifying drugs are good examples of specific "targeted" therapy. These agents improve airway function and asthma control, with effects on inflammatory components of asthma such as LTs, eosinophils, and cytokines (56, 57). They have also been associated with decreased need for steroid rescue and improved quality of life.

About 55 to 60% of patients with asthma respond well to these LT-modulating drugs; the rest do not. Differentiating factors have not been fully identified, but the results suggest that all asthma is not alike. Further investigations into specific "targeted" therapy will likely reveal similar responder/nonresponder groups.

There are many novel therapies for asthma in various stages of development. Inhibitors of phosphodiesterase IV, believed to work by raising intracellular calcium levels through increases in cAMP, have been effective in animal models of asthma. Monoclonal antibodies directed against T cells have shown promise in clinical trials involving patients with severe steroid-dependent asthma. Monoclonal antibodies that remove IL-5 from active participation in cell activation have shown a profound effect on eosinophilia and airway reactivity in animal models of asthma, and human studies are underway. Other promising approaches include monoclonal antibodies against IgE, IL-4 receptor antagonists, and antitachykinin agents.

The pharmacokinetics and pharmacodynamics of therapy for rhinitis were outlined. It was noted that a number of basic questions regarding pharmacotherapy either have not been investigated or have been studied only superficially. Issues addressed included topical versus systemic drug administration; nasal drug distribution and absorption; drug effect on target cells, end organs, tissues, symptoms, and disease; and future prospects.

The benefits of topical drug administration for rhinitis include low systemic toxicity, quick onset of action, and good effect. Drawbacks include inability to reach all mucous membranes, and varying patient compliance. The availability of nasal corticosteroids that can be administered once daily has improved patient compliance.

There are few studies on the effects of delivery system characteristics on the clinical response to intranasal medication (58). It is not known what effect nasal hypersecretion, sneezing, and partial nasal blockage have on drug accessibility to target cells. There are few comparisons between pressurized aerosols and aqueous pump sprays, and their results cannot be predicted on the basis of knowledge of mucosal drug distribution. Any drug delivered to the nose should be hydro-

philic to dissolve in the mucous layer, and lipophilic to be absorbed through cell membranes. The total process must be completed within 20 to 30 min, before drug is removed by mucociliary clearance. Spraying in a sneezing or dripping nose will probably reduce efficacy. On the other hand, inflammation seems to have no effect on the absorption, bioavailability, or efficacy of intranasal medication (59).

Intranasal corticosteroids reduce sensitivity of sensory nerves, plasma exudation, vasodilatation, secretory reactivity of glands, and the number of goblet cells (60, 61). Drug development has focused on intranasal corticosteroids that are not absorbed and have better intranasal distribution. A major question, still unanswered, is whether a topically applied nasal corticosteroid can have an antiasthmatic effect without being absorbed.

Systemic corticosteroids have a relatively poor effect on sneezing and rhinorrhea, a marked effect on nasal blockage (62, 63), an excellent effect on olfaction, and some effect on paranasal sinuses. Few placebo-controlled studies of systemic corticosteroids in rhinitis have been conducted, and studies are needed to examine the effect of systemic treatment when topical therapy is insufficient, in nasal polyposis with anosmia, for common cold-induced exacerbations, pre- and postsurgery, and to determine effects on quality of life. No studies have demonstrated an additive effect of topical and systemic medication, and there are no dose-response studies to guide the correct choice of dosage.

The H₁ antihistamines target sensory nerves, parasympathetic reflexes, seromucous glands, and exchange and capacitance vessels in the nose. Antihistamines have been shown to be effective at inhibiting experimentally induced early-phase sneezing, and reduce sneezing and rhinorrhea in allergic rhinitis (64). Although antiinflammatory actions of H₁ antihistamines have been demonstrated experimentally (65-67), these effects do not appear to be significant clinically.

Several other therapeutic agents for rhinitis were reviewed. Topical administration of α -adrenoceptor agonists, although effective, is limited to 1-2 wk because of the risk of rhinitis medicamentosa. The therapeutic index of oral α -agonists is low. Ipratropium bromide effectively controls watery rhinorrhea, but not mucopurulent secretions, sneezing, or blockage (68). The role of LT-modifying drugs for the treatment of rhinitis remains to be demonstrated.

The efficacy of concomitant therapies for asthma and rhinitis was reviewed next.

The controversy regarding the role of histamine and antihistamine therapy in asthma was addressed. Dating back to Herxheimer, investigations have demonstrated a role for histamine in the clinical manifestations of asthma (69-71): histamine stimulates smooth muscle contraction, chemotaxis of eosinophils, secretion of mucus, and increased vascular permeability. Although there are individual studies with antihistamines demonstrating improvement in airway function, asthma symptoms, and quality of life, there are not enough convincing data to recommend that H₁ antagonists be used for the treatment of asthma. Objective measures of asthma control have not consistently improved. Despite some studies demonstrating benefit, the consensus was that there are not enough data to support their widespread use in perennial asthma (72, 73). It was emphasized that histamine is not the only mediator responsible for asthma symptoms. Thus, antihistamines should be considered as adjunctive therapy for asthma. However, there is a clinical impression that control of allergic rhinitis symptoms with antihistamines may facilitate asthma control. Thus, at least as regards H₁ histamine antagonists, the nose and lungs are not similar.

The similarities and differences regarding the use of allergy immunotherapy for rhinitis and asthma were reviewed. Although allergy immunotherapy dates to 1911, when Noon first described its use for allergic rhinitis (74), there is still doubt about its use for asthma (75, 76). The mechanism(s) by which immunotherapy works in allergic diseases remains unknown. Furthermore, there are unique differences between rhinitis and asthma that make clinical studies of asthma more difficult to perform and interpret. However, immunotherapy is still the only method of treatment beyond total avoidance of an allergen that may prevent disease and reverse the disease process with long-term benefit (77).

Studies concerning the mechanism(s) of efficacy of allergy immunotherapy for rhinitis and/or asthma should consider the differences and similarities between these diseases. Rhinitis involves a small tissue area, the nose, and possibly sinuses, and upper airways that are primarily dependent on tissue congestion after a vascular leak and airway edema for symptoms. On the other hand, asthma has been characterized by smooth muscle contraction in conjunction with factors such as bronchial and neurogenic hyperresponsiveness, airway epithelial damage and sloughing, and cellular inflammation and edema with smooth muscle hypertrophy, all of which decrease airway size and lower the threshold for airway hyperresponsiveness. Mediators of rhinitis and asthma appear to be similar, but asthma is significantly affected by other factors, such as recurrent or chronic sinusitis, gastroesophageal reflux, upper airway obstruction, and recurrent or intercurrent viral infections. Although these factors may also apply to rhinitis, they are not as significant. The "link" between the upper and lower airways may be the key to understanding treatment of rhinitis or asthma with allergy immunotherapy.

Many studies have proven the efficacy of allergy immunotherapy for rhinitis, including double-blind, placebo-controlled studies (78–82). Efficacy has also been shown for asthma, including one study of ragweed immunotherapy (83). Other studies, primarily associated with dust mite and mold exposure, have been summarized in a metaanalysis (84). The odds ratio for improvement in asthma symptoms increased significantly. However, doubt still lingers about the clinical importance of the benefit of allergy immunotherapy for asthma and particularly about what role immunotherapy should play in asthma treatment. This is exemplified by a study of young children growing up in the inner city or suburban areas of the Eastern seaboard of the United States (85) that failed to show efficacy. However, both the control group and treatment group consisted of growing children, many of whom would improve with age; cockroach antigen was not present in the mix; and subjects were eliminated if they did not comply with avoidance and use of medications. Thus, the question became not whether allergy immunotherapy for asthma was effective, but whether additional benefit could be detected when immunotherapy was added to medications and avoidance. A perennial question concerning immunotherapy is whether the correct antigens are being used (85).

The safety of immunotherapy continues to be a major deterrent to its use, including concerns about anaphylactic reactions and death. However, safety can be improved if patients with asthma are not given allergy immunotherapy when they have asthma flares, if the dose is reduced when starting new vials and "in season," and if rush immunotherapy is administered together with antihistamines. However, if immunotherapy can modify the natural course of the disease, as has been suggested (75), then the risk may be justified. The guidelines published by the World Health Organization (WHO), the National Heart, Lung, and Blood Institute (NHLBI), and the

Global Initiative for Asthma currently recommend that only patients with asthma who have house dust mites as their major perennial allergens should be treated with immunotherapy. However, others advocate a broader use of immunotherapy for asthma (86). For rhinitis, the cost is less for immunotherapy compared with equal control with medications. For asthma, the difference is greater, owing to the high cost of medications.

Further studies are needed to explore the link between rhinitis and asthma and the benefits of allergen immunotherapy. Problems that remain include the large number of allergens that may be relevant in some patients, the possibility of a placebo effect, and the need to standardize extracts. Other new methods of immunotherapy to be tested include oral and peptide immunotherapy, anti-IgE antisense for various mediators and peptide receptors, and DNA vaccines. The latter two have been shown to downregulate receptors and bronchial hyperresponsiveness or to reverse Th2 predominance with enhancement of IL-12 production in animal models. These agents may modulate allergic inflammation of asthma and rhinitis, and the pruritus, edema, and endothelial vascular leak of rhinosinusitis.

The use of leukotriene modifiers for the treatment of asthma and/or rhinitis was reviewed. Data exist suggesting that leukotrienes are involved in the pathophysiology of both conditions. Early studies of patients with asthma demonstrated that LT modifiers shift the dose–response curve to inhaled leukotrienes, and inhibit experimentally induced bronchoconstriction. More recent clinical trials with zileuton, zafirlukast, pranlukast, and montelukast have shown benefit in clinical asthma, an effect that is additive to that of β -agonists or inhaled steroids, and a steroid-sparing effect (56, 87, 88).

Although cells that synthesize leukotrienes are similar in the upper and lower airways, few studies of leukotriene modifiers in the upper airways have been conducted. Donnelly and coworkers described a reduction in nasal congestion and rhinorrhea by zafirlukast (89), and Knapp reported reduction of nasal congestion due to allergen challenge in patients pretreated with zileuton (90).

It was emphasized that the role of LT modifiers in allergic rhinitis needs further evaluation. The potential value of combination products containing antagonists of both leukotrienes and histamine in a single oral tablet was stressed as deserving study.

Clearly, areas of consensus, but also of controversy, exist regarding concomitant therapies for asthma and rhinitis. There is a strong link between allergic rhinitis and asthma, and both can be caused by allergic and nonallergic triggers. However, the efficacy of common treatments for these two diseases is more controversial.

Other therapeutic agents that have effects in both the nose and the lungs include corticosteroids and theophylline. The former has effects in both the upper and lower airways. Some data suggest that topical nasal corticosteroids can have an effect on the lower airways. Regarding the latter, theophylline is reported to reduce inflammation in the nose after allergen challenge (91), but it has not been used routinely for rhinitis.

In summarizing the effects of drugs in rhinitis and asthma, it was concluded that the nose and lungs can function as either a single organ, or as two different entities, depending on the mediator targeted, the route of drug administration, and on factors not yet known. Summary recommendations included the following:

1. Published recommendations for immunotherapy (78, 92, 93) are in many cases separate for asthma and rhinitis, and this artificial separation has led to unresolved issues (76, 77). The group thought it important to consider the use of immunotherapy when allergen sensitization is an important part of the pathophysiological process. In allergic rhinitis,

immunotherapy is indicated for patients in whom antihistamines and topical medications do not provide adequate control, patients who do not wish to use pharmacotherapy, and patients in whom pharmacotherapy produces undesirable side effects (78). In allergic asthma, immunotherapy is indicated for patients with mild disease, those in whom symptoms are not adequately controlled by allergen avoidance and pharmacologic treatment, patients with both nasal and bronchial symptoms, those who do not wish to be on long-term pharmacotherapy, and patients in whom pharmacotherapy has produced undesirable side effects (78).

2. H₁ blockers represent the first-line treatment of allergic rhinitis, but they are not recommended for the control of asthma (94, 95).
3. Leukotriene modifiers are effective in controlling symptoms of mild to moderate asthma when used as primary or adjunct treatment and limited studies suggest that they may be effective in the treatment of rhinitis. They therefore have the potential to treat asthma and rhinitis, but more data are needed to evaluate fully their effect.

CONCLUSION

(*Stephen C. Lazarus, M.D., workshop cochair*): In summary, identifying a population of patients who have both asthma and allergic rhinitis is not difficult. Much of the debate during the workshop centered on the extent to which the pathophysiology of the two diseases overlaps; that is, their similarities and differences, and whether treating one will affect the other. While more questions were raised than resolved, scientific investigation in the near future will help fix the relative position of these diseases to each other, leading to more definitive statements about effector cells and nerves and the ways in which these overlap and interact in their functions. At present, therapy can either be directed at all, or at individual, components of these functions. What will be important in determining which therapy to choose and how best to target novel therapies is understanding not only the extent to which the cytokines, mediators, and nerves interact, but the extent to which asthma and allergic rhinitis overlap with each of these.

Practitioners appear to have different perspectives on the epidemiology of allergic rhinitis and asthma when treating adults versus children. A 30- or 40-yr-old patient who has a completely developed immune system and history of asthma provides a different perspective than a young wheezing child for whom contributing factors have not yet been delineated. This can result in significantly different conclusions about the natural history of these diseases and about what constitutes critical (disease-precipitating) events that happen at a very early age compared with what is seen in the adult population.

(*Thomas B. Casale, M.D., workshop chair*): One clear message from the 2-d workshop, which is supported by the National Institutes of Health asthma guidelines (42), is that it is important for physicians who care for patients with asthma alone or rhinitis alone to consider both upper and lower airways when treating either disease. The guidelines emphasize that treatment of upper respiratory tract symptoms is an integral part of the management of asthma, with intranasal corticosteroids recommended for the treatment of chronic rhinitis in patients with persistent asthma.

Throughout the workshop, discussions centered on whether asthma and allergic rhinitis represented one airway and one disease, or two airways and two diseases. From the data presented, there is evidence to support both arguments: both diseases have similar pathogenic mechanisms, they often occur together, and a specific therapy may treat both diseases effec-

tively; however, they also may be quite different. For example, epithelial shedding and airway remodeling appear to be important features of asthma but not allergic rhinitis. A more accurate conclusion is that the "one airway one disease" paradigm is too naive and simplistic. For example, there are many different types of asthma. Patients may have exercise-induced syndrome, nonallergic asthma, or allergic asthma. There are also many distinct rhinitic syndromes characterized by different triggers, pathogenic mechanisms, and histologic changes. For example, vasomotor rhinitis and allergic rhinitis are distinct entities. This suggests that asthma and rhinitis should not be viewed as a single disease with different target organs.

However, another view that should be considered is that allergic asthma and rhinitis represent a systemic disease affecting two organs, the lung and nose. Asthma and allergic rhinitis share many of the same pathogenic factors, but they operate in different parts of the airway. Inflammatory cells and mediators are often the same, and there may be common alterations that occur in the immune system. An elevated IgE level occurs not only in asthma and allergic rhinitis, but in other allergic conditions as well. Neural transmitters are the same, although they have different effects in the upper and lower airways. In fact, data suggest that people with atopic disease also have similar hyperresponsiveness in the gut. There appear to be common genetic predisposing factors for the development of both diseases. Both have been associated with abnormalities in the autonomic nervous system, many of which have been shown to be systemic in nature (38, 39). For example, cholinergic hyperresponsiveness has been shown not only in the lung, but in the skin and eyes of patients with asthma and allergic rhinitis. Patients with these diseases have peripheral blood eosinophilia, not just lung or nasal eosinophilia. Finally, therapy that works for both diseases tends to be systemic in nature, such as the LTRAs, antihistamines, anti-IgE, and allergen immunotherapy.

In conclusion, there are many important features of the immunobiology of asthma that overlap with rhinitis. Furthermore, the epidemiology of these diseases suggests many common factors involved in their high coincidental occurrence. Despite scientific advances, however, much about these diseases remains unknown, such as whether treating or neglecting to treat rhinitis ultimately affects the course of asthma. With the advent of newer therapeutic modalities, better knowledge about the control of both diseases should be forthcoming.

Acknowledgment: This conference was initiated by the Allergy, Immunology, and Inflammation Scientific Assembly of the American Thoracic Society.

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