

Introduction

Through numerous lines of investigation it has become apparent that inflammation plays a critical role in the pathogenesis of asthma and rhinitis and the genesis of clinical respiratory symptoms. Once inhaled, allergic and nonallergic stimuli trigger key immune effector cells to release mediators and cytokines that ultimately mediate vascular dilation and edema, epithelial damage, mucus secretion, smooth muscle contraction and hypertrophy, and subepithelial fibrosis, all of which are found in varying degrees in people with asthma. Furthermore, the release of mediators and cytokines can affect neurogenic pathways important in regulating airway and vascular tone and mucus release. Similar biologic events occur in the upper airways subsequent to inhalation of allergens and certain irritants.

A workshop was convened as a program of the American Thoracic Society Assembly on Allergy, Immunology and Inflammation to review the immunobiology of asthma and rhinitis. The workshop, held in Montreal, Quebec, Canada, in June 1997, brought together many participants from several countries. The goal of the workshop was to develop a consensus statement describing commonalities and differences between asthma and rhinitis with regards to 1) pathogenesis (in the context of the structure and function of the upper and lower airways), including immune effector cells and mediators and 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 disease, or interrelated conditions; and 3) treatment, with a focus on distinct therapy as well as current and future concomitant therapies. Plenary sessions provided state-of-the-art lectures. Discussion then took place in four workshops:

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 Co-Morbidity of Asthma and Rhinitis, and
4. Current Therapies and Future Prospects for the Concomitant Treatment of Asthma and Rhinitis.

A general session allowed each workshop moderator time to present a statement developed from participant discussion.

In Part I of the workshop proceedings, which follows, participants summarized the pathogenic factors relating to asthma and rhinitis. Part II focuses on these two conditions from an epidemiologic perspective and includes therapeutic options.

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ragweed challenge ⁽¹²⁾. Factors responsible for determining whether an individual has allergic rhinitis alone rather than rhinitis and asthma are poorly understood.

b) Factors Contributing To Differences In Pulmonary Versus Nasal Responses

A number of diverse factors could contribute to differences in the allergic response as manifested in the lung versus the nose (Table 2).

The most obvious of these is the central role played by airway smooth muscle in the lung. In addition to a contractile response, airway smooth muscle could play other roles in asthma. It has recently been shown that activated BAL T cells, recruited to the lung by segmental antigen challenge, both adhere to cultured human airway smooth muscle cells and up-regulate the expression of intracellular adhesion molecule (ICAM)-1 and HLA-DR on airway myocytes ⁽¹³⁾. In addition, treatment of human airway smooth muscle cells with TNF- α and IFN- γ led to the production of a strong bioactivity chemotactic for eosinophils, subsequently identified as RANTES ⁽¹⁴⁾. Small amounts of subepithelial collagen could also conceivably play a much more important role in the lung than in the nose. Increased nonspecific airway reactivity is also associated with allergic rhinitis, and it could play a role in that disease. In addition, the demonstration that "priming" of the nose by exposure to nitrogen dioxide produced eosinophil degranulation, as shown by an increase in ECP levels in nasal lavage fluid after nasal antigen challenge by a formerly subthreshold dose of allergen ⁽⁷⁾, suggests that such "heterologous" priming could be an important factor to amplify inflammatory responses in the nose. It is also likely that different mediators are more important in pulmonary versus nasal responses. For example, histamine appears to play a much more important role in allergic rhinitis than in allergic asthma. Conversely, one could speculate that cysteinyl leukotrienes are likely to be more important in asthma than in rhinitis, although some relief of symptoms associated with seasonal allergic rhinitis has been reported with a leukotriene (LT) D4 receptor antagonist ⁽¹⁵⁾.

Differences in airway geometry, surface area, and blood supply(ies) in the lung and the nose are also potentially important factors that could result in differences in pulmonary versus nasal inflammatory responses. While such differences and exposure to environmental triggers are readily apparent, 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. Following segmental antigen challenge of a person who had ragweed allergic asthma, there was a marked pulmonary eosinophilia lasting at least 7 days and an increase in BAL GM-CSF for more than 14 days after challenge ⁽¹⁶⁾. While there exist no comparable data for the kinetics of the resolution of an IgE-mediated inflammatory response in the nose, one could speculate that mechanical factors would likely lead to considerably more rapid clearance of inflammatory cells and mediators in the nose in comparison with the lung. In unpublished studies (Hastie and Peters), it has also been observed that repair of damage to airway epithelium produced by segmental antigen challenge and harvesting of bronchial epithelial cells by brush biopsy requires 14 days or longer, as indicated by expression of genes needed for terminal differentiation of epithelial cells (the β dynein heavy chain of cilia). Again, it is not known whether repair of nasal epithelium requires a similar amount of time, but this is another potential difference between the nose and lung.

In conclusion, the basic machinery necessary to develop an IgE-mediated inflammatory response after antigen exposure is likely to be similar in subjects with rhinitis only and in those with asthma and rhinitis; i.e., in the nose and in the lung. Differences in nasal versus pulmonary responses are likely due to structural and physiological differences, some of which have been discussed here, plus factors that produce asthma in some individuals but not others, which are poorly understood at present.

CC family, located on chromosome segment 7q11- q21, contains several eosinophil-selective chemokines. These include RANTES, MCP-1a, MCP-3, and eotaxin ⁽²¹⁾.

Accumulating evidence supports the importance of leukocyte and vascular endothelial cell adhesion molecules in the migration of inflammatory cells, including eosinophils, into tissue sites during allergic reactions. This involves a sequence of events that includes margination of leukocytes along the walls of the microvasculature, adhesion to the endothelium, transmigration through the vessel walls, and migration along a chemotactic gradient within the extravascular compartment that contains extracellular-matrix proteins such as fibronectin. These events are mediated by adhesion molecules such as integrins, selectins, and members of the immunoglobulin gene superfamily ⁽²²⁾.

Intercellular adhesion molecule (ICAM)-1, VCAM-1, and E-selectin are three representative endothelial adhesion molecules. ICAM-1, a ligand for the b2 integrin molecules LFA-1 and Mac-1, which are present on the surface of leukocytes, mediates the attachment of all classes of leukocytes to endothelial cells. ICAM-1 is known to be expressed constitutively on vascular endothelial cells and can be induced by inflammatory mediators on other extravascular cells. E-selectin binds to sialyl Lewis X, which is expressed on the surface of leukocytes. VCAM-1 supports the adhesion of leukocytes to endothelial cells through interactions with the integrin molecule very late activation antigen (VLA)-4 (a4b1), which is present on the surface of lymphocytes, monocytes, eosinophils, and basophils, but not neutrophils. VCAM-1 expression can be selectively induced on the endothelium by treatment with IL-4.

Montefort and colleagues ⁽²³⁾ observed increased expression of ICAM-1 and VCAM-1 in nasal mucosal biopsy specimens from subjects with perennial allergic rhinitis, compared to that in normal controls. Lee and colleagues ⁽²⁴⁾ confirmed the constitutive expression of ICAM-1 on the vascular endothelium in nasal biopsy specimens. They also showed that the percentage of vessels expressing VCAM-1 is upregulated 24 hours after allergen challenge, and that E-selectin is modestly upregulated, whereas ICAM-1 is not.

Because the counter ligand for VCAM-1, VLA-4, is present on eosinophils, but not on neutrophils, it is speculated that the upregulated VCAM-1 contributes, at least in part, to the selective recruitment of eosinophils into the nasal mucosa after antigen provocation.

One result of the cellular influx after antigen stimulation and the release of proinflammatory mediators is a change in responsiveness of the upper airway to a second stimulus. The change can be specific (increased responsiveness to the same antigen) or nonspecific (increased reactivity to irritants). The change in nonspecific reactivity is usually shown by challenge with histamine or methacholine.

Increased responsiveness to antigen, i.e., priming, occurs after provocation as well as during seasonal exposure. The increased sensitivity to antigen that follows a prior antigen challenge is related to inflammation, but is not obligatorily linked to it; thus, inflammation can occur in the absence of priming.

Anonallergic form of inflammation can be induced by inhalation of cold, dry air. Studies on the mechanism of cold, dry air-induced rhinitis have shown elevations in the osmolality of nasal secretions postchallenge ⁽²⁵⁾. Antigen challenge of the upper airway causes an increased responsiveness to cold, dry air (Figure 3). This demonstrates the additive effect of two naturally occurring triggers of symptoms.

The epithelium, like the skin, has long been considered to be a barrier between the external

The factors responsible for the accumulation of CD41 T cells in atopic states are many and interact in complex networks to yield the inflammatory reactions seen in atopic rhinitis and asthma. While products of mast cells, CD41 T cells, and epithelial cells are important, in all models of these diseases the presence of CD41 T cells appears to be essential for the inflammatory processes to occur. Thus, the factors that modulate CD41 T cell accumulation (such as IL-16) and the products of CD4 cells are of paramount importance in understanding these diseases and targeting new therapies.

4. Leukotrienes As Mediators Of Upper And Lower Airway Obstruction

Jeffrey M. Drazen, M.D. (Brigham and Women's Hospital in Boston, Massachusetts): The leukotrienes are a family of polyunsaturated lipoxygenated eicosatetraenoic acids that are derived from arachidonic acid and exhibit a wide range of pharmacological and physiological actions (32,33). In biological systems, their actions are limited by their relative rates of synthesis and degradation (34,35). Of the three enzymes exclusively involved in the formation of the leukotrienes—namely, 5-LO, LTC₄ synthase, and LTA₄ epoxide hydrolase (Figure 4)—5-LO is the enzyme required for the production of both the cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄), and LTB₄. Over the past decade, 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. Under basal conditions, 5-LO is found in soluble form in the nucleus and cytosol; however, when the host cell is activated, the enzyme translocates to the perinuclear membrane, where it becomes catalytically active (36).

Prior to the structural identification of the leukotrienes, it had been established that slow-reacting substance of anaphylaxis (SRS-A) was a potent contractile mediator for isolated airway smooth muscle (37). Shortly after its chemical structure was found to be comprised of the cysteinyl leukotrienes, LTC₄ and LTD₄ were identified as potent contractile agonists for isolated human airway smooth muscle and in intact humans (38-42). The cysteinyl leukotrienes are 3,000 to 10,000 times more potent as bronchoconstrictor substances than histamine or methacholine. Leukotrienes have also been shown to increase mucus production, mediate mucosal edema, and aid in the recruitment of eosinophils in an epithelium-dependent manner, critical pathophysiologic events in asthma and rhinitis (43). These observations heightened interest in the role of the cysteinyl leukotrienes as mediators of asthma (44). However, the most convincing data for the role of the leukotrienes in asthma and rhinitis are based on the observation that inhibition of the synthesis or action of the leukotrienes is associated with an improvement in disease control (43,45-50). Of particular relevance is the observation from these studies that the 30% to 90% inhibition of 5-LO activity achieved by zileuton is associated with clinically significant improvements in asthma outcome. This finding indicates that log-order changes in 5-LO action are not required to effect a clinical response and that changes on the order of twofold in 5-LO enzyme action are of physiological interest.

Although it has been known for some time that 5-LO is a critical enzyme in the metabolic pathways leading to the production of the leukotrienes, only in the past 3 to 5 years has evidence accrued from clinical studies indicating that 5-LO action plays a pivotal role in the biology of human disease, especially asthma. Indeed, it is reasonable to conclude that an understanding of the regulation of the action of 5-LO will have important implications for understanding the biology of asthma. It is known that the catalytic action of 5-LO leads to irreversible loss of enzyme function and that maintenance of 5-LO activity requires de novo synthesis of 5-LO. However, the mechanisms regulating the expression of the 5-LO gene and the translation of 5-LO mRNA into a

and constricts bronchial and vascular smooth muscle. TxA2 causes bronchial and vascular constriction and platelet aggregation. PGD2 is a bronchoconstrictor, causing pulmonary vasoconstriction and increased vascular permeability and platelet aggregation. PGF2a causes bronchoconstriction and platelet aggregation, and PGE2 acts as a vasodilator, causing mucus secretion and inhibition of inflammatory cell function.

Cysteinyl leukotrienes, mainly LTC4, are synthesized and released by eosinophils. They mediate a variety of responses in the human lung and when applied exogenously cause several symptoms resembling typical features of clinical asthma, including bronchoconstriction, increased vascular permeability, mucus secretion, and cellular infiltration ^(54,55).

The eosinophil and eosinophil mediators discussed above have also been implicated in the pathogenesis of allergic rhinitis. The release of lipid mediators in the upper airway can cause or contribute to many of the pathophysiologic features characteristic of allergic rhinitis, including edema, mucus production and rhinorrhea, and inflammation.

6. Workshop Consensus

Alan R. Leff, M.D. (University of Chicago, Chicago, Illinois): The consensus discussion was limited to models of allergic asthma and allergic rhinitis because these two diseases are currently better defined than nonallergic asthma and rhinitis and sufficient comparisons could be made. For example, in the allergic situation, a response can be provoked with a known stimulus and the influx of cells and consequent events studied. In the nonallergic situation, i.e., perennial rhinitis or nonatopic asthma, determining pathophysiology is more difficult, largely because of the problematic nature of provoking the actual sequence of events when the particular stimulus corresponding to that in nature remains unknown. However, the participants agreed that nonallergic rhinitis, nasal polyposis, and sinusitis should continue to be studied as models of inflammation because they may have some correlation with lower respiratory conditions not elaborated upon during the workshop. In particular, nasal polyposis associated with intrinsic asthma and aspirin intolerance provides a model for examining eosinophilic airway inflammation and the role of leukotrienes.

One difference between atopy and asthma is that 20% of the U.S. population can be defined as having atopic rhinitis, whereas only 5% has asthma. However, atopy itself is not well defined. If definitions include a positive skin test or the presence of IgE, then the actual incidence of atopy may be higher than that reported. The 4:1 ratio of those with allergic rhinitis vs allergic asthma alone was discussed in the context of inflammatory cells common to both conditions. Without prioritizing in order of importance, these include the epithelium (as a transducer rather than an ameliorating cell in asthma), mast cells and basophils, T cells (particularly the CD41 line), eosinophils, and neutrophils.

Similarities and differences between the epithelium in the upper and lower airways were outlined. Characteristics in common include the generation of chemotactic factors (e.g., MIP-1a, IL-8, and IL-16) and importance in mucus secretion. The secretory response to inflammatory mediators was believed to be similar; thus, products with an effect on the 5-LO pathway could block or resolve both upper and lower airway events simultaneously.

Differences in the upper and lower airway epithelium include shedding, a greater degree of heterogeneity in the lung, duration of inflammation, antigen distribution in nature, and histamine response. 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 in the upper airways. If the epithelium produces substances involved in bronchoconstrictor response, sloughing would in some way terminate or ameliorate that response. There is no analogy in the nose or sinuses. Greater

can act either as a bronchodilator or a bronchoconstrictor. Recent evidence indicates that adhesion molecules on airway smooth muscle have counter ligands corresponding to those on inflammatory cells. However, the precise role of these adhesion molecules in upregulating the constrictor response or bringing inflammatory cells in closer proximity to the airway smooth muscle is not yet understood physiologically.

The effects of the products of inflammatory cells on the end organ in allergic rhinitis and asthma were also discussed. In asthma, the production of leukotrienes and other substances causes edema, which may have an important augmentative role in inducing lumen narrowing via airway wall thickening. Bronchoconstriction is unique as a mechanism of obstruction in the lower airways; there is no comparable muscle constrictor response in the nose. Mucus plugging can be quite harmful in severe asthma, whereas it is not a major mechanism of obstruction in allergic rhinitis. In contrast, the predominant mode of obstruction in rhinitis is vascular engorgement, mediated in large part by nitric oxide. As previously discussed, the effect of histamine is also much more important in the nose.

The workshop group concluded with a discussion of critical areas for future research and a series of unanswered questions that focused on asthma phenotypes, triggers for atopy and nonallergic rhinitis and asthma, pathogenic differences in atopic and nonatopic disease, and the precise relationship between inflammation and hyperresponsiveness in rhinitis.

Regarding asthma phenotypes, the issue of specific components of leukotriene-dependent asthma and the genetic expression of existing mutations in the population of the 5-LO promoter gene were discussed. One question was whether bi-modal responses to leukotriene therapy existed or was instead a Gaussian distribution, as is found with other medications; i.e., a highly responsive and a not very responsive group.

The group also noted that the ability to define the arachidonic cascade and the cells responsible for asthma and rhinitis still does not answer the question of what starts and continues the process. For example, 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?

In attempting to define the relationship between inflammation and hyperresponsiveness for rhinitis, often no clear correlation exists. In a vasomotor condition, for example, there is substantial rhinitis but little inflammation; this is also seen in severe asthma, where the inflammatory cell presence does not always correlate with the severity of the condition. Thus, separate from the issue of allergy and nonallergy, what is the precise relationship between inflammation and the clinical conditions of rhinitis and hyperresponsiveness?

Finally, why do some patients not respond to therapy, specifically steroids? None of the participants believed that this could be explained on the basis of any yet known specific phenotype or on the basis of some morphological airway change unique to the group of nonresponders versus responders.

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of Diseases [ICD] coding system.) There do appear to be clear increases in hospitalization rates that are most pronounced in children from birth to age 4 years. Rates per 1,000 were 3.2 in 1979 and 5.5 in 1990, representing almost a 50% increase in these very young children. Results are slightly less dramatic in children from birth to age 17 years, for whom the rates have increased from 1.6 in 1979 to 2.8 in 1990 ⁽¹²²⁾.

d) Trends In Asthma Mortality

Asthma mortality rates in the United States are very low. The current rate for persons of all ages is 1.9 per 100,000, which is substantially lower than the rates in the mid-1950s, although there has been a slight increase in the past 10 years. This increase can be ascribed, in part, to ICD coding changes. Overall, it would appear that there has been little clear increase in asthma mortality ⁽¹²¹⁾.

However, asthma prevalence and health care usage have increased in the United States. There are two possible explanations for this increase in asthma prevalence and morbidity: access to health care and changes in risk factors.

e) Access To Health Care

Currently, approximately one third of people at or near the poverty level in the United States are without health insurance. Children and single mothers who are on Medicaid report greater asthma morbidity. Recent studies suggest that asthma mortality in urban, mostly minority populations, approximates the highest asthma mortality rates anywhere in the world. These data suggest that access to health care, and in particular, access to the use of highly effective inhaled antiinflammatory medications, is likely to be less among the urban poor. Antiinflammatory therapy can cost an estimated \$60 to \$100 per month. Even families with health insurance who lack adequate medication coverage may be unable to afford appropriate medication. While the reduction in morbidity by inhaled corticosteroid use has not been clearly demonstrated, there seems to be little question that these medications are useful in decreasing both symptoms and health care use. Clearly, lack of access to health care could be contributing to the increased prevalence and morbidity of asthma in the United States.

f) Changes In Risk Factors

Although overall prevalence of current cigarette smoking has decreased in both men and women in the United States, among women of childbearing age, particularly poor women, cigarette smoking has actually increased. Maternal cigarette smoking is known to be associated with the development of asthma in early childhood, but the changes in maternal smoking rates are not sufficient to account for the increase in asthma prevalence and morbidity. Most importantly, there has been a growing recognition of the importance of the indoor environment and indoor allergens in the development of asthma. House dust mites, fungi (*Alternaria*), cockroaches, cats, and dogs are all important sources of allergens. It appears that different allergens are important in different populations; e.g., house dust mites are present in most carpeted homes in temperate climates, whereas cockroaches appear to be more prevalent in inner city dwellings. Although the relative importance of these indoor allergens as causal factors in childhood asthma is still being studied, it seems unlikely that allergens alone are contributing to the increase in asthma. Premature birth is a known risk factor for the development of asthma. Increased success in salvaging low birth-weight infants has resulted in viability of infants as small as 1,000 grams. These low birth-weight infants are known to be predisposed to bronchopulmonary dysplasia and subsequent asthma and increased airway reactivity. The absolute numbers of these infants are small, and thus are probably not contributing in any substantial way to an increase in asthma prevalence.

It has previously been thought that viral infections, particularly respiratory syncytial virus, can

patients tend to have psychological problems, such as extreme introversion, shyness, and preference for being alone. In addition, there is an association with depression, fearfulness, and fatigue. Adolescents also report a higher degree of concern for bodily functions and have a poorer general adjustment in dealing with environmental pressures. Not surprisingly, mood and cognitive impairments have been associated with chronic rhinitis. It is well known that asthma develops more commonly in patients with chronic rhinitis (58% of adults with seasonal allergic rhinitis) and asthma is 3 to 5 times more common in seasonal allergic rhinitis than nonallergic rhinitis. An association with sinusitis and rhinitis is well known. Additionally, chronic snoring and significant orthodontic problems in children are found more often in patients with chronic rhinitis.

In summary, chronic rhinitis is one of the most common chronic disorders that affect the general population. It afflicts individuals in their most productive years, is expensive to manage, and is associated with significant co-morbidities such as sinusitis, asthma, and chronic otitis.

3. Early Allergic Rhinitis As A Risk Factor For Childhood Asthma

Anne L. Wright, Ph.D. (University of Arizona, Tucson): Rhinitis is the most common manifestation of allergic disease, affecting about 20 million people in United States. In addition to being an important clinical entity on its own, some studies have shown an association between allergic rhinitis in childhood and asthma (131-133).

Data from the Tucson Children's Respiratory Study provide support for this association (134). Parents completed questionnaires regarding respiratory symptoms and risk factors for asthma at a mean age for their children of 1.6, 2.9, and 6.2 years. They were asked whether their child had "ever had hay fever or any other condition that made his/her nose runny, stuffy or itchy," and whether a doctor ever said this was due to allergic rhinitis.

By the age of 6 years, 37% of children had never been diagnosed with rhinitis; 63% had received that diagnosis. Of the children with rhinitis, two-thirds had been told by a doctor that these symptoms were due to allergies. Children with physician-diagnosed allergic rhinitis had significantly more respiratory symptoms, such as wheeze, compared to those with nonphysician-diagnosed allergic rhinitis and no rhinitis (54%, 37%, and 32%, respectively, p , 0.00001) and cough without a cold (65%, 52%, and 37%, respectively, p , 0.00001). In addition, they had more symptoms associated with their rhinitis, and were significantly more likely to take rhinitis medications more than rarely (42% vs 28% for children with nonphysician-diagnosed allergic rhinitis, p , 0.05). Atopy was also significantly more common among children with physician-diagnosed allergic rhinitis compared to children with nonphysician-diagnosed allergic rhinitis or those without rhinitis (50%, 25%, and 33%, respectively, p , 0.00001). Finally, the percent of children with asthma was 3% for children with no rhinitis, 6% for those with nonphysician-diagnosed allergic rhinitis, and 18% for children with physician-diagnosed allergic rhinitis (p , 0.00001). The association of physician-diagnosed allergic rhinitis with asthma was independent of atopy, as both atopic children and those without atopy at age 6 were significantly more likely to have asthma if they had physician-diagnosed allergic rhinitis.

For half of children who developed physician-diagnosed allergic rhinitis, symptoms began in the first year of life. This early onset of physician-diagnosed allergic rhinitis was associated with more respiratory symptoms, greater medication use, and a higher prevalence of asthma by age 6 years. Incidence of asthma (defined as physician-diagnosed with associated wheeze and/or "asthma symptoms") by age 11 years was significantly higher for children with onset of physician-diagnosed allergic rhinitis in the first year of life. 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, even after adjusting for other risk factors, including parental asthma history, eosinophilia at 9 months, eczema in infancy, male gender, and atopy by age 6

because of deposition of collagen in the submucosa, a factor which would in turn perpetuate the disease. Using retrospective chart review, a longitudinal epidemiologic study from Rochester, Minnesota ⁽¹³⁵⁾ has found that in those 30, 40, or 50 years of age who have symptoms of asthma, these symptoms can be traced to their first year of life.

A frequently asked question is, does rhinitis cause asthma? Some data have indicated that the early development of rhinitis and symptoms of asthma are associated with a common risk factor for both: a decreased production of interferon-g in 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 differently, 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 that are either present or absent and predispose the children to develop changes in the lower airway that lead to the asthmatic phenotype. These alterations 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 hyperresponsiveness and some characteristic of the lung, altered by the environment with respect to immune reactivity, produces asthma ⁽¹³⁶⁾.

Hypotheses regarding genetic predisposition are supported by multivariate analyses. Hazard ratios associated with cumulative incidence of developing asthma, after correcting for all possible phenotypic factors that would represent allergy or inflammation in the airway, demonstrate that maternal and paternal physician-diagnosed asthma (2.0 and 2.0, respectively) remain strong independent risk factors for the development of asthma. In comparison, the hazards ratio for male gender is 1.6 and atopy by 6 years, 2.4. Thus, independent of the development of immune responses in the airways, something specific is inherited that is associated with an increased risk for asthma. Ongoing studies already 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.

Finally, combining both genetic and environmental factors, Shirakawa et al. ⁽¹³⁶⁾ have demonstrated that certain infections may considerably alter the nature of immune reactivity. In their study of a tuberculin test in patients ages 6 and 12 years, those who became tuberculin-positive either by or after the age of 6 years had a dramatically lower prevalence of atopy and of asthma at the age of 12 years than subjects who did not. This points to both a genetic factor and a possible environmental factor; i.e., this phenotypic pattern may have been due to a genetically determined exuberant Th1 response, or an environmental tuberculin exposure that resulted in a preferential Th1 response. In either case, these factors appeared to influence significantly the subsequent development of atopy and asthma in these children.

In conclusion, 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 (Figure 9). Future research will delineate the extent to which these factors exist and contribute to the development of allergic rhinitis with or without asthma.

B. Current Therapies And Future Prospects For The Concomitant Treatment Of Asthma And Rhinitis

such as nuclear factor kappa-b (NF-kb) and activating protein-1 (AP-1), among others. These "transcription factors" activate the transcription of genes, and glucocorticoids are potentially involved in regulating their effects on the genome. Whatever the final mechanism, glucocorticoids are known to have profound inhibitory effects on cytokine production, and it is through this pathway that they are now believed to inhibit cellular migration⁽¹³⁹⁾. Glucocorticoids also increase the apoptosis of eosinophils and decrease the half-life of eosinophils in the tissue, as well as decreasing influx. The effects on the production of lipid mediators are much less clear, and in certain systems corticosteroids may upregulate enzymes such as cyclooxygenase and 5-lipoxygenase.

(2) Specific Targeted Therapy: Leukotriene (LT) Modifiers

The newest additions to the asthma treatment armamentarium are the LT modifiers, which can be further divided into leukotriene receptor antagonists (LTRAs) and 5-lipoxygenase (5-LO) enzyme inhibitors. This is the first time that a specific component of asthmatic inflammation has been successfully targeted for drug intervention. Leukotrienes are important mediators of asthma, with the cysteinyl LTs LTC₄, LTD₄ and LTE₄ known to be potent bronchoconstrictors, modulators of mucus production and clearance, and inducers of edema formation. Leukotriene B₄ is a potent neutrophil and eosinophil chemoattractant and activator. Leukotriene receptor antagonists have a direct effect on the actions of the cysteinyl LTs, while 5-LO inhibitors prevent the formation of LTB₄ and the cysteinyl LTs. Data from the LTRAs suggest that these drugs are bronchodilators, with additional long-term effects on inflammatory components of asthma, such as the LTs themselves, eosinophils, and potentially cytokines^(140,141). The 5-LO inhibitors have similar effects, but have also shown both a decrease in the need for steroid rescue and a prolonged "trough effect," suggesting that even when drug is no longer present in the body, a long-term effect on airway obstruction has been achieved. Additionally, there are decreases in both peripheral and pulmonary eosinophils with LT modifiers.

An important aspect of LT modulating drugs is the observation that about 55% to 60% of asthmatics respond very well to these drugs, whereas the rest do not. The reasons behind these differences in response are not clear and differentiating factors have not been described. However, these results suggest that all asthma is not alike and further investigations into "targeted" therapy for asthma are likely to reveal similar responder/nonresponder groups. Eventually, a better understanding of the disease may permit therapy to be tailored to match the specific syndrome that is present.

b) Future Therapies

(1) Nonspecific Therapy

(a) Phosphodiesterase IV Inhibitors

These drugs are believed to work by raising intracellular calcium levels through increases in cAMP. These drugs have been very effective in animal models; however, further studies are needed in humans to determine whether the animal models will be predictive of effects in human asthma.

(b) Anti-T-Cell Antibodies

T-cells are believed by many people to be the orchestrators of asthmatic inflammation. Efforts to decrease T-cell numbers through use of monoclonal antibodies have shown promise in clinical trials involving severe steroid-dependent asthmatics.

(2) Specific Therapy: Anti-Interleukin-5

(1) Intranasal Corticosteroids

The effects of intranasal corticosteroids on target cells are summarized in (Table 3) (147,148). Probably as an indirect consequence of reduced release of cytokines and mediators, topical corticosteroid treatment results in 1) reduced sensitivity of sensory nerves, 2) reduced plasma exudation from exchange vessels, 3) reduced vasodilatation, 4) reduced secretory reactivity of glands, and 5) reduced number of goblet cells.

Future prospects for intranasal corticosteroids include developing drugs that are not systemically absorbed and have better intranasal distribution while minimizing risk of local side effects. These attributes will result in better dosing schedules and better patient compliance.

It is still an open question whether a topically applied nasal corticosteroid can have an anti-asthmatic effect without being absorbed. There are now a number of placebo-controlled studies showing a beneficial effect of intranasal corticosteroids on asthma symptoms in pollen allergy (149, 150,151). The clinical implications are uncertain, but the potential interaction between upper airway inflammation and lower airway symptoms is interesting.

(2) Systemic Corticosteroids

The effects of systemic corticosteroids on target tissue and symptoms include a relatively poor effect on sneezing and rhinorrhea, a marked effect on nasal blockage (152), an excellent effect on olfaction, and some effect on paranasal sinuses.

Few placebo-controlled studies have been conducted on the effect of systemic corticosteroids in rhinitis. No studies to date have demonstrated an additive effect of topical and systemic medication, and there are no dose-response studies to guide the correct choice of dosage. It is likely that many patients would benefit from short-term treatment with systemic steroids and long-term basic treatment with topical steroids.

(3) H1-Antihistamines

The H1-antihistamines target the sensory nerves, the parasympathetic reflex and seromucous glands, and the exchange and capacitance vessels. Blood vessels possess H1 receptors but H1-antihistamines have little effect on nasal blockage. The most important effect is probably mediated via sensory nerve H1 receptors. Antihistamines have been demonstrated in clinical trials to be profoundly effective on early-phase sneezing; however, they are less effective on late-phase symptoms and on blockage. It is not yet known what effect they have on the underlying disease process.

In allergic rhinitis, a major reduction in sneezing and rhinorrhea can be obtained with antihistamine alone, in contrast to blockage, which primarily responds to corticosteroids (Table 4) (153).

The antiinflammatory properties of the H1-antihistamines have been demonstrated in experimental research, including the ability of terfenadine and loratadine to inhibit nasal histamine release (154,155) and of cetirizine to inhibit upregulation of epithelial ICAM-1 (156).

If a second generation antihistamine really had an antiinflammatory effect of clinical significance, then the drug would be expected to have the following effects: (1) a reduction in the number of Langerhan's cells, Th cells with a Th2 cytokine profile, epithelial mast cells, or mucosal eosinophils, (2) a better clinical effect than a first generation antihistamine; e.g., chlorpheniramine, (3) a marked effect on nasal blockage, and (4) a significant effect on bronchial asthma. To our

approximately 15%, which was comparable to the effect of aminophylline. There was also a significant but smaller improvement after oral chlorpheniramine and, as expected, no improvement after butabarbital or placebo.

Groggins et al. ⁽¹⁶²⁾ studied 10 children ages 8 to 14 years for the bronchodilator effect of 2, 4, and 8 mg of inhaled chlorpheniramine. All treatment groups improved peak expiratory flow and FEV_{0.75} at 2 minutes, which progressed over the next 30 to 45 minutes. However, chlorpheniramine was poorly tolerated and caused an irritant reaction in 13 of 30 occasions, characterized by a fall in peak expiratory flow.

b) Azelastine

Tinkelman and colleagues ⁽¹⁶³⁾ showed improvement in FEV₁ and decreased use of bronchodilator therapy with azelastine. Spector et al. have shown that the bronchodilator properties of azelastine could be observed in a dose-related matter ^(164,165).

c) Ketotifen

Ketotifen, which has both antihistaminic as well as cromolyn-like properties, has been investigated as a possible alternative to cromolyn due to its long-acting oral properties. In a double-blind Canadian study of 138 children with the goal of reducing other medication, 60% of the patients in the ketotifen group were able to stop using theophylline, compared with 34% in the placebo group. There was a significant improvement in the global score of well-being ⁽¹⁶⁶⁾.

Another study of 50 asthmatic patients receiving 1 mg and 2 mg of ketotifen found no improvement in pulmonary function, although a significant reduction in albuterol use was seen in those patients who were not taking inhaled corticosteroids ⁽¹⁶⁷⁾.

The major side effect in these patients has been sedation. However, weight gain was also described following prolonged administration, as were minor side effects such as headache, dry mouth, bronchospasm, and dizziness.

d) Terfenadine

Initial studies with terfenadine involved doses that are now considered unsafe due to the accumulation of the free terfenadine ^(168,169). Spector and colleagues studied 60 mg and 120 mg terfenadine in patients with concomitant rhinitis and asthma and found a significant bronchodilator effect relative to placebo, which lasted at least 8 hours after a single dose ⁽¹⁷⁰⁾. After 2 weeks of twice daily terfenadine therapy, the bronchodilatory effect was reduced, although patients showed no worsening of their asthma symptoms. This study may have pointed out the value of a wash-out period of antihistamines prior to doing such studies if, in fact, tolerance to the bronchodilator effect can develop.

e) Cetirizine

Bousquet et al. ⁽¹⁷¹⁾ studied 97 patients with asthma and rhinitis secondary to grass pollen exposure. Patients received either 10 mg or 15 mg of cetirizine twice daily, 60 mg terfenadine twice daily, or placebo. Only the subjects taking 15 mg cetirizine showed improvement in symptoms, as measured by the pooled total symptoms scores.

Spector et al. ⁽¹⁷²⁾ examined the effects of cetirizine in a double-blind, placebo-controlled study of

Recently, emphasis has been placed on inflammation in rhinitis, sinusitis, and asthma. This concept of the allergic inflammatory response evolved from the rekindling of interest in early-phase and late-phase responses and a reaffirmation of the presence of inflammation in both rhinitis and asthma following allergen challenge. Modification of the late-phase response with immunotherapy has been demonstrated in several studies in adults as well as in children (Table 5).

Late-phase responses in asthma are characterized by two significant factors: cellular inflammation—especially eosinophils and neutrophils, lymphocytes, platelets, and monocytes following a single allergen challenge—and bronchial hyperresponsiveness (BHR), which can subsequently increase for days, weeks, or even months (Figure 10) (183). Thus, cellular inflammation and BHR characterize asthma and are probably associated in most situations. However, it has been recognized that BHR and inflammation can be disassociated. This emphasizes the potential for genetic polymorphism, which exists within atopic diseases.

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 primarily involves a small tissue area, the nose, and possibly sinuses, and upper airways that are primarily dependent upon tissue congestion following a vascular leak and airway edema for symptoms. On the other hand, asthma has been characterized primarily by smooth muscle contraction in conjunction with factors such as neurologic 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 disease (GERD), upper airway obstruction (including vocal cord dysfunction), and recurrent or intercurrent viral infections (Table 6). Viral infections, for example, have been shown to enhance late-phase responses, airway inflammation, and subsequent BHR (Figure 11). 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 efficacy of allergy immunotherapy for rhinitis (184-188); in general, double-blind, placebo-controlled studies have all shown efficacy for both rhinitis and asthma (Table 7). For asthma, a recent study with ragweed demonstrated immunotherapy was effective (207). Other studies worldwide have been summarized in a meta-analysis primarily associated with dust mite and mold exposure (208). The odds ratio for improvement in asthma symptoms was increased significantly (Figure 12). However, doubt still lingers about the therapeutic benefit of allergy immunotherapy for asthma. This is exemplified by a recent study of young children growing up in the inner city or suburban areas on the Eastern seaboard (209). This study failed to show efficacy for broad-spectrum immunotherapy as it is "done in the clinic." However, several significant flaws in this study soon became apparent: 1) both control group and treatment group were growing children, many of whom would normally improve with age; 2) cockroach antigen was not present in the mix (cockroach has been recently shown to be highly associated with urban asthma (210) and at least half of these children were living in urban settings); and 3) the subjects were eliminated from the groups if they did not comply with avoidance of allergens and use of medications. Thus, the question became not whether allergy immunotherapy for asthma was effective, for which there were definite trends, but whether or not additional benefit from allergy immunotherapy added to medications and avoidance could be detected.

The safety of immunotherapy continues to be a major deterrent to its use. Concerns about anaphylactic reactions and death are still present. However, safety can be improved if asthmatics are not given allergy immunotherapy when they have asthma flares. The dose of immunotherapy must be reduced when starting new vials and "in season" (e.g., during ragweed season in patients

Many large multicenter, parallel-design, double-blind clinical trials have been conducted with the LTRA zafirlukast ^(211,214,217). These have shown a significant dose-dependent increase in morning peak flow and FEV₁, a significant decrease in the night-time awakenings, a significant dose-dependent decrease in the need for rescue bronchodilator treatments, and a decrease in both daytime and night-time asthma symptom scores ^(140,217).

Tamaoki et al. ⁽²¹⁸⁾ examined the role of pranlukast in 79 adults with severe steroid-dependent asthma requiring greater than 1,500 mg beclomethasone dipropionate per day. After a 2-week run-in baseline period, the dose of inhaled beclomethasone was reduced by 50%, and the patients were then randomized to either pranlukast 450 mg bid or placebo bid for 6 weeks. At week 6, patients taking placebo showed a progressive and significant decrease in their morning and evening peak expiratory flows, while those taking pranlukast showed no change. Similarly, the daytime and night-time asthma symptom scores significantly increased in the placebo group, whereas those taking pranlukast showed no deterioration in symptoms or increase in the need for inhaled beta agonists.

Serum eosinophil cationic protein (ECP) increased significantly following reduction in the beclomethasone dose in the placebo-treated group, whereas in the patients on pranlukast, there was no change. Exhaled nitric oxide levels also progressively and significantly increased in the individuals on placebo, whereas those in the pranlukast group demonstrated no significant change in this parameter.

These studies are also consistent with the suggestion of an antiinflammatory component of pranlukast; further studies support this finding. Diamant et al compared the effect of inhaled LTD₄ and methacholine on sputum cell differentials in asthma ⁽²¹⁹⁾. LTD₄ induced eosinophilia in the sputum of asthmatic subjects 4 hours after inhalation, suggesting that LTD₄ recruits eosinophils into the airways of asthmatics in vivo. However, some patients challenged with methacholine also showed an increase in sputum eosinophils.

Cells that synthesize leukotrienes are similar in the upper and lower airways, including mast cells, basophils, eosinophils, monocytes, and macrophages; therefore, it seems somewhat surprising that so few studies of leukotrienes in the upper airways have been conducted. In one such study, Bisgaard et al. ⁽²²⁰⁾ demonstrated a significant rise in LTC₄ in the tear fluid following ocular allergen challenge. A subsequent study by Skoner et al. ⁽²²¹⁾ showed that nasal washings assayed before and during the grass pollen season in grass-sensitive allergic rhinitics had an elevation in LTC₄ levels during the grass season that correlated with increases in nasal resistance and pollen counts. Studies by Knani et al. ⁽²²²⁾ were conducted in patients with perennial allergic rhinitis who underwent nasal lavage to determine if having symptoms or positive skin tests affected leukotriene levels in nasal washings. These studies showed that LTC₄ and LTD₄ levels were undetectable or low in the control group of nonallergic patients, whereas patients who were allergic and symptomatic had significantly higher levels of LTC₄ and LTD₄ than control patients.

Donnelly et al. ⁽²²³⁾ reported the results of a double-blind, parallel-group, placebo-controlled trial in 164 patients with seasonal allergic rhinitis and documented sensitivity to ragweed. Patients were divided into 5 groups of 33 subjects, each receiving either 10, 20, 40, or 100 mg of zafirlukast or placebo, and spent 2 consecutive days in a park during the ragweed season, when pollen counts were high. Mean symptom scores were determined at three different times: 1) while in the park; 2) after leaving the park while at home; and 3) for the entire day. For the 20, 40, and 100 mg doses, nasal congestion was reduced on day 1 and 2, and symptom scores were lower than placebo for all three endpoints. Rhinorrhea symptom scores were significantly lower than placebo for endpoint 2 on day 1 for the 10, 20, and 40 mg doses, and on day 2 for the 20 and 40 mg doses; these scores were significantly lower than placebo for all three endpoints. Sneezing symptom scores on day 1

There is a link between allergic rhinitis and asthma, and asthma and rhinitis can be caused by allergic and nonallergic triggers. Asthma and rhinitis can be associated both with an IgE-mediated allergic reaction and an inflammatory pattern. However, the efficacy of treatment is more easily proven for allergic rhinitis than for asthma, especially when airways remodeling is present. Allergen sensitivity versus exposure is also a factor; i.e., pollen is less common a trigger in asthma than in allergic rhinitis. In chronic asthma, cockroach is a major allergen in some areas of the United States, but not for most of Europe. Seasonal exposures may also differ, and there are confounding variables, especially for asthma (e.g., rhinitis, sinusitis, and GERD).

One important question is whether the correct antigens are being used in immunotherapy. For example, house dust mite allergens are standardized and easy to use, but this is not true for cockroach allergens. This was evident in a recent study by Adkinson ⁽²⁰⁹⁾, and may be one of the factors that led to a negative outcome. Cat allergen is good choice for immunotherapy, but molds present problems, with fewer molds being used as immunotherapy in Europe than in the United States.

In patients with asthma, the major problem with immunotherapy is safety. Most of the patients who have had lethal reactions to immunotherapy had severe asthma, and the reaction was primarily bronchial. The prevalence of reactions range from 0.3% per injection up to 20% during the build-up phase in some rush immunotherapy trials. With the availability of safe and effective drugs for asthma, the question arises, is immunotherapy sufficiently effective for asthma to warrant the risk? Most of the published literature has demonstrated efficacy, but it is known that some unfavorable studies have not been published. One key is patient classification and characterization. Dr. Metzger demonstrated objectively that the late-phase response seen in asthma after *Alternaria* challenge was almost completely ablated after 1 year of immunotherapy. Treatment of children, however, warrants caution, because whatever their age, sensitivity, or severity of disease, the use of multiple allergens will result in failure.

One unique advantage of immunotherapy is that it may modify the natural course of the disease. In a recent case-controlled study ⁽¹⁸⁴⁾ in which children between the ages of 3 and 6 years were followed for 3 years from baseline, all children who did not receive immunotherapy had new sensitizations, whereas only 50% of the children with immunotherapy developed new sensitizations. Further studies are needed to confirm these results. The Preventive Asthma Study, conducted in Scandinavia and Germany, also suggests that the development of asthma is less likely to occur in patients with allergic rhinitis who are treated with immunotherapy. After 1 year, 20% of control subjects had asthma, compared with 10% of those who had had immunotherapy. However, a study in adults with perennial asthma showed immunotherapy to be less effective in patients 30 years of age and older and in those believed to have permanent alteration of airways structures, as demonstrated by FEV₁ less than 70% of predicted.

The guidelines published by the World Health Organization, the National Heart, Lung, and Blood Institute, 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 ⁽²²⁷⁾. Efficacy and safety studies suggest that patients with nonspecific triggers or an irreversible airflow obstruction; i.e., an FEV₁ less than 70% of predicted value, be treated instead with pharmacotherapy.

Generally, it has been concluded that H1 blockers are not recommended for the treatment of asthma. Objective measures of asthma control have rarely been improved with H1 blockers. They also have potential side effects, especially the first-generation agents. However, Dr. Spector pointed out that histamine has many potentially important effects, both on the nose and on the

The indications for immunotherapy in allergic asthma and rhinitis have been separated in some guidelines (229,230). This artificial separation has led to unresolved issues (176,177), possibly because the allergen-induced IgE-mediated reaction has not been considered to be a multi-organ disease. It is important to consider immunotherapy based on the allergen sensitization rather than on the disease itself.

In allergic rhinitis (184), immunotherapy is indicated for subjects in whom antihistamines and topical medications do not provide adequate control of symptoms; who do not wish to use pharmacotherapy; in whom pharmacotherapy produces undesirable side effects; and who do not desire to receive long-term pharmacologic treatment.

In allergic asthma (184), immunotherapy is indicated for subjects who do not present with a severe form of the disease (FEV₁ levels should be greater than 70% of predicted values after adequate pharmacologic treatment); in whom symptoms are not adequately controlled by allergen avoidance and pharmacologic treatment; who have both nasal and bronchial symptoms; who do not wish to be on long-term pharmacotherapy; and in whom pharmacotherapy produced undesirable side effects.

Medications for asthma and rhinitis may be administered via local (nasal or bronchial), oral, and parenteral routes. The major advantages of delivering drugs directly into the nose and lower airways are that high concentrations can be delivered more effectively into the target organ and systemic side effects are avoided or minimized (230,231). Moreover, some drugs like cromoglycate or nedocromil are not absorbed when given orally and are effective only when administered locally. In patients suffering from asthma and rhinitis, local administration of drugs requires that they be given both nasally and bronchially and this may decrease compliance with treatment, which is already low in asthma and rhinitis. On the other hand, drugs administered by the oral route may have an effect on both nasal and bronchial symptoms and would be expected to have a higher patient compliance rate.

The topical treatment of rhinitis using corticosteroids has been found to improve asthma. Symptoms and pulmonary tests (231) were improved, and exercise-induced asthma (150) or bronchial hyperresponsiveness (151,152) were reduced. These data suggest that treating nasal inflammation may help to control asthma.

H1-blockers represent the first-line treatment of allergic rhinitis, but they are not recommended for the control of asthma (232,233). Leukotriene modifiers are effective in controlling symptoms of mild to moderate asthma and some limited studies have suggested 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 fully evaluate their effect on asthma and rhinitis. Theophylline was found to reduce nasal inflammation (228). It has also been observed that theophylline can reduce bronchial hyperresponsiveness in patients with nasal symptoms (234). Oral corticosteroids are highly effective in the treatment of rhinitis and asthma, but side effects after long-term use are common.

IV. Conclusion

A. Dr. Lazarus' Perspective

Stephen C. Lazarus, M.D. (University of California, San Francisco, San Francisco, California), Workshop Co-Chair: 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; i.e., their similarities and differences, and whether treating one will affect the other. While more questions were raised than resolved,

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 recent scientific advances, however, much about these diseases remains unknown, such as whether treating or neglecting to treat rhinitis affects the course of asthma. With the advent of newer therapeutic modalities, better knowledge about the control of both diseases should be forthcoming.

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