

Allergic rhinitis and asthma: How important is the link?

Jonathan Corren, MD Los Angeles, Calif.

Dysfunction of the upper and lower airways frequently coexist, and they appear to share key elements of pathogenesis. Data from epidemiologic studies indicate that nasal symptoms are experienced by as many as 78% of patients with asthma and that asthma is experienced by as many as 38% of patients with allergic rhinitis. Studies also have identified a temporal relation between the onset of rhinitis and asthma, with rhinitis frequently preceding the development of asthma. Patients with allergic rhinitis and no clinical evidence of asthma commonly exhibit nonspecific bronchial hyperresponsiveness. The observation that management of allergic rhinitis also relieves symptoms of asthma has heightened interest in the link between these diseases. Intranasal corticosteroids can prevent increases in nonspecific bronchial reactivity and asthma symptoms associated with seasonal pollen exposure. Similarly, among patients with perennial rhinitis, daily asthma symptoms, exercise-induced bronchospasm, and bronchial responsiveness to methacholine are reduced after administration of intranasal corticosteroids. Antihistamines, with or without decongestants, reduce seasonal rhinitis symptoms, asthma symptoms, and objective measurements of pulmonary function among patients with rhinitis and asthma. The mechanisms that connect upper and lower airway dysfunction are under investigation. They include a nasal-bronchial reflex, mouth breathing caused by nasal obstruction, and pulmonary aspiration of nasal contents. Nasal allergen challenge results in increases in lower airway reactivity within 30 minutes, suggesting a neural reflex. Improvements in asthma associated with increased nasal breathing may be the result of superior humidification, warming of inspired air, and decreased inhalation of airborne allergens. Postnasal drainage of inflammatory cells during sleep also may affect lower airway responsiveness. A link between allergic rhinitis and asthma is evident from epidemiologic, pathophysiologic, and clinical studies. Future research, however, is needed to determine whether nasal therapy can alter the natural history of asthma. (J Allergy Clin Immunol 1997; 99:S781-6.)

Key words: Allergic rhinitis, asthma, bronchial hyperresponsiveness, intranasal corticosteroids, antihistamines, decongestants

The apertures of the nose, how marvelously they come next after the sponglike (ethmoid) bone . . . and how the connection was cut through into the mouth at the palate in order that inspiration may not begin in a straight line with the trachea and that the air entering it may first be bent and convoluted, so to speak. For I think this should be double advantageous: the parts of the lung will never be chilled when oftentimes the air surrounding us is very cold, and the particles of dust . . . will not penetrate as far as the trachea. Galen, 2nd century AD, "On the Usefulness of the Parts of the Body."

Practicing physicians and clinical investigators have long noted a relation between allergic rhinitis and bronchial asthma. Dysfunction of the upper and lower airways frequently occur together and appear to share key elements of pathogenesis. Despite the strong clinical association between these diseases, it remains controversial whether rhinitis serves as a risk factor for the development of asthma and whether active nasal disease can affect lower airway symptoms and function. These

and other issues have practical implications for clinicians who treat patients with chronic respiratory allergy.

In this review, the association between allergic rhinitis and bronchial asthma is examined through a review of data from epidemiologic, clinical, and laboratory studies. Potential areas of future research to aid understanding of this relation are highlighted.

EPIDEMIOLOGIC STUDIES: COEXISTENCE OR CAUSE-AND-EFFECT?

A large number of cross-sectional studies have demonstrated that rhinitis and asthma commonly occur together. Nasal symptoms have been reported among 28% to 78% of patients with asthma,¹⁻³ compared with approximately 20% of the general population.⁴ Similarly, as many as 19% to 38% of patients with allergic rhinitis may have asthma,^{1,3} much more than the 3% to 5% prevalence among the general population.⁵ In a survey of 6563 residents, new diagnoses of probable allergic rhinitis or asthma were two- to fourfold higher among persons who previously had one of these diseases compared with persons who had no history of either disease.⁶

The onset of rhinitis and asthma may be temporally related. In a study involving children 13 to 17 years old

From the Allergy Research Foundation, Inc.
Reprint requests: Dr. Jonathan Corren, Allergy Research Foundation, Inc., 11620 Wilshire Blvd., Suite 200, Los Angeles, CA 90025.
Copyright © 1997 by Mosby-Year Book, Inc.
0091-6749/97 \$5.00 + 0 1/0/79127

with both rhinitis and asthma, 59% either had nasal symptoms first or had symptoms of both diseases appear during the same year.⁷ A similar study involving college students revealed that 64% had rhinitis before the onset of asthma and that 21% had both upper and lower airway disease at the same time.⁸ In a study involving 7662 patients with a broad range of ages, 49% of patients with both rhinitis and asthma had nasal symptoms first, and 25% had both diseases within 1 year of each other.³ These studies suggest that rhinitis frequently precedes asthma and that upper airway dysfunction may be a predictive factor for subsequent development of lower airway disease. However, because these are cross-sectional studies based on patient recall, the data cannot be considered conclusive. In 1994 Settipane et al. reported the results of a prospective, 23-year follow-up study involving 690 college freshmen who had no evidence of bronchial asthma.⁹ Students who reported nasal symptoms in 1961 were three times more likely to have asthma (10.5%) than participants without rhinitis (3.6%).

Multiple investigations have shown that patients with allergic rhinitis and no clinical evidence of asthma commonly exhibit nonspecific bronchial hyperresponsiveness. Comparisons of these data are difficult because the studies were performed with a variety of methods for bronchial provocation and used different definitions of hyperresponsiveness. One early report suggested that as many as 73% of patients with nasal allergies demonstrated increased airway responsiveness to methacholine or histamine.¹⁰ Data collected more recently show that between approximately 11% and 32% of patients with rhinitis have positive bronchoconstrictor responses to histamine, methacholine, or carbachol that are in the range of responses observed in patients with asthma.¹¹⁻¹³ Among patients with seasonal hay fever and no asthma, airway responsiveness may increase markedly during seasonal periods of pollen exposure. Madonini et al. examined 27 patients with seasonal rhinitis before and during the pollen season. The investigators documented that the incidence of bronchial hyperresponsiveness rose from 11% before to 48% during the pollen season.¹¹ In addition, patients with perennial allergic rhinitis appear to have higher levels of lower airway responsiveness than patients with seasonal nasal allergy.¹⁴ Some investigators have suggested that bronchial reactivity in the asthmatic range (i.e., methacholine PC₂₀ <8 mg/mL) may help to identify patients with rhinitis who are at risk for asthma.^{13, 15} However, one study demonstrated that bronchial hyperresponsiveness was not useful in predicting which patients with rhinitis would subsequently have asthma.¹⁶

It is difficult to determine whether rhinitis is the first manifestation of respiratory allergy for a patient who may eventually have asthma or whether nasal disease is playing a direct role in causing asthma. Long-term epidemiologic studies of patients with allergic rhinitis, including assessments of bronchial responsiveness, will be critical in answering this question. In addition, results

from therapeutic and laboratory research studies will help to provide insights into this question.

CLINICAL TRIALS: THE EFFECTS OF NASAL THERAPY ON ASTHMA

In anecdotal experience, physicians have often noted improvements in asthma after successful treatment of rhinitis. Until recently, however, few controlled clinical trials have been attempted to measure this effect. Since the mid 1980s, several investigators have begun to evaluate carefully the impact of rhinitis therapy on asthma symptoms, pulmonary function, and airway responsiveness.

Intranasal corticosteroids

Studies have demonstrated minimal deposition of intranasal corticosteroids into the lungs, restricting the therapeutic effects of these agents to the upper airway.^{17, 18} Therapeutic trials of these rhinitis-specific medications, therefore, are useful in assessing the effects of nasal dysfunction on asthma. A number of trials have been conducted to examine the efficacy of intranasal corticosteroids for patients with both seasonal and perennial allergic disease of the upper and lower airways.

Welsh et al. compared use of intranasal flunisolide, beclomethasone dipropionate, cromolyn, and placebo in patients with ragweed hay fever.¹⁹ In addition to measuring nasal symptoms, the investigators also assessed chest symptoms in a small subgroup of patients who had seasonal asthma. Rhinitis scores improved among patients receiving active treatment (i.e., either of the two corticosteroids or cromolyn); however, both of the intranasal corticosteroids were more effective than cromolyn. In addition, asthma symptoms were virtually eliminated in the two groups receiving intranasal steroids compared with subjects taking cromolyn and placebo (Fig. 1). My coworkers and I later sought to confirm these findings in a study of the use of intranasal beclomethasone dipropionate by patients with seasonal allergic rhinitis and asthma.¹⁷ Bronchial responsiveness to inhaled methacholine, measured before and at the peak of the fall pollen season, increased in a statistically significant way among patients receiving placebo but did not change among patients receiving active treatment. However, there were no differences in asthma symptoms, peak expiratory flow rates, or spirometric indices between the active therapy and placebo groups. Although both these trials involved small numbers of patients, the results suggest that prophylactic treatment with intranasal corticosteroids can prevent increases in nonspecific bronchial reactivity and asthma symptoms associated with seasonal pollen exposure.

Similar investigations have focused on patients with perennial nasal allergy and asthma.^{18, 20} In a 4-week trial of use of intranasal budesonide by patients with perennial rhinitis and asthma, chronic nasal obstruction improved and mouth breathing decreased with active therapy.²⁰ With these changes in nasal function, daily asthma symptoms were reduced and exercise-induced broncho-

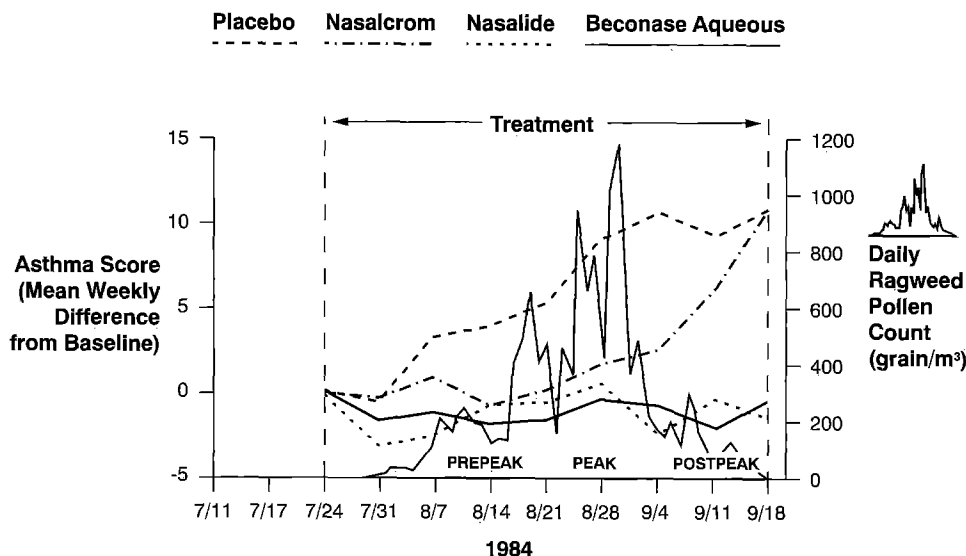


FIG. 1. Mean weekly scores for symptoms of asthma, adjusted for baseline values among 58 patients with seasonal asthma. Daily ragweed pollen count is shown by the jagged solid line with corresponding values on the right-side y axis. (From Welsh et al. Mayo Clin Proc 1987;62:125-34.)

spasm, assessed by means of treadmill testing, was markedly attenuated. In a subsequent study involving patients with mite-induced rhinitis and asthma, Watson et al. evaluated the effects of intranasal beclomethasone dipropionate on asthma, including an assessment of bronchial responsiveness to methacholine.¹⁸ After 4 weeks of active treatment, airway responsiveness was reduced by approximately a twofold dilution compared with baseline. The investigators also performed a radio-labeled deposition study of the corticosteroid aerosol and found that less than 2% of the drug was deposited into the chest area. These two trials demonstrated that intranasal corticosteroids are effective in improving chest symptoms and nonspecific airway responsiveness in patients with established, chronic nasal inflammation. The results of the study by Watson et al. also suggested that the reduction in asthma is due to improvement in nasal function rather than direct effects on the lower airways.¹⁸

Another study that requires comment compared the effects of intranasal versus intrabronchial (by means of oral inhalation) administration of beclomethasone dipropionate 400 µg/day on lower airway reactivity in patients with rhinitis and no asthma.²¹ After 2 weeks of therapy, intranasal delivery of the corticosteroid caused marked improvement in bronchial responsiveness, whereas oral inhalation had no effect on reactivity. Because intranasal administration was far more effective than oral inhalation of the corticosteroid, these data suggest that nasal inflammation plays a key role in modulating lower airway responsiveness associated with allergic rhinitis. Long-term studies involving patients with perennial rhinitis and bronchial hyperreactivity will help determine whether asthma can be prevented among

some persons by means of early treatment with intranasal corticosteroids.

Antihistamines

Histamine has been identified as a mediator of potential importance in allergic asthma.²² Histamine type 1-receptor antagonists have been shown to have direct effects on lung function.²³ Clinical trials with these drugs have demonstrated variable improvement in lower airway symptoms and function.²⁴⁻³⁰ Therefore, unlike those of intranasal corticosteroids, the salutary effects of antihistamines on asthma cannot be ascribed solely to improvements in upper airway function.

Studies of first-generation antihistamines demonstrated minimal improvement in bronchial asthma.³⁰ Initial small-scale trials of second-generation drugs included small numbers of patients and yielded mixed results.²⁴⁻²⁹ In general, reductions in lower airway symptoms were observed only when larger than approved doses of antihistamines were used (e.g., terfenadine 240 to 540 mg per day^{24, 25} and cetirizine 15 to 20 mg per day^{27, 28}). Two multicenter trials have been conducted with antihistamines in approved doses; the results indicated improvement in asthma symptoms.^{29, 31} Grant et al. demonstrated that cetirizine, 10 mg once a day, reduced the severity of seasonal rhinitis and asthma symptoms; however, objective measures of pulmonary function were not statistically different from those of placebo.²⁹ In a study in which loratadine 5 mg plus pseudoephedrine 120 mg was administered twice a day to patients with seasonal rhinitis and asthma, my co-workers and I demonstrated that asthma symptoms, peak expiratory flow rates, spirometry, and asthma-specific quality of life all improved in a statistically

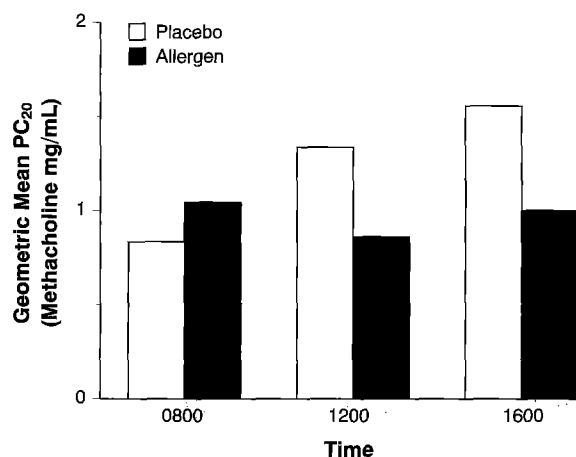


FIG. 2. Effect of nasal challenge on bronchial responsiveness, expressed as the geometric means of PC₂₀ to inhaled methacholine; $p = 0.011$ at 1200 (12 PM) and $p < 0.0009$ at 1600 (4 PM), comparing change from baseline 1800 (8 AM) for placebo versus allergen ($n = 10$ for both treatments). From Corren J et al. *J Allergy Clin Immunol* 1992;89:611-8.

significant way among patients taking active therapy.³¹ The inclusion of decongestant therapy in this trial may have had clinically significant effects on asthma by restoring the filtration function of the nose. Antihistamines, with and without decongestants, appear to be useful adjuncts in treating patients with seasonal allergic rhinitis and concomitant asthma.

LABORATORY RESEARCH: EXPLORING THE MECHANISMS

Although there is compelling evidence that allergic rhinitis may influence the clinical course of asthma, the mechanisms connecting upper and lower airway dysfunction are poorly understood. A variety of theories have been proposed to explain the apparent relation between nasal disease and asthma. These theories include (1) the existence of a nasal-bronchial reflex, (2) mouth breathing caused by nasal obstruction, and (3) pulmonary aspiration of nasal contents.

Nasal-bronchial reflex

Dating back to 1919, Sluder postulated that asthma was caused by a neural reflex originating in the nose.³² This hypothesis underwent rigorous testing with a variety of animal models in the early 1960s. These experiments demonstrated that nasal irritation can result in reflex bronchoconstriction,³³ reflex bronchodilation,³⁴ or no change in lower airway function,³⁵ depending on the type of animal and stimulus selected. In 1969, Kaufman et al. applied silica particles onto the nasal mucosa of human subjects without asthma and found marked and immediate increases in lower airway resistance.³⁶ Bronchospasm induced by nasal silica was blocked by both systemic administration of atropine³⁶ and resection of the trigeminal nerve,³⁷ suggesting that the effect was caused by a cholinergic reflex. Similar

findings of rapid-onset bronchoconstriction were reported by other groups who used nasal petrolatum packing³⁸ and cold air application³⁹ as the provocative substances.

Yan and Salome later performed nasal histamine challenges for persons with perennial rhinitis and stable asthma and found that FEV₁ was reduced by 10% or more immediately after provocation for 8 of 12 subjects.⁴⁰ Although the results of the study supported the role of nasal histamine in causing changes in the lower airway, several other laboratory challenge studies that used histamine⁴¹⁻⁴³ and allergen⁴¹⁻⁴⁵ did not demonstrate bronchoconstriction. My coworkers and I investigated the effects of nasal allergen provocation on baseline lower airway caliber and nonspecific bronchial responsiveness to methacholine.⁴⁵ Ten persons with seasonal allergic rhinitis and asthma were selected for the study; all patients related worsening of asthma to the onset of hay fever symptoms. There were no changes in baseline spirometry, specific conductance, or lung volumes measured 30 minutes and 4 hours after the induction of a nasal allergic response. Nonspecific bronchial responsiveness, however, increased significantly 30 minutes after nasal challenge and persisted for 4 hours (Fig. 2). Because radionuclide studies demonstrated no evidence of allergen deposition into the lungs, it seems unlikely that these increases in airway reactivity can be attributed to direct effects of allergen. In addition, the rapidity with which these changes occurred suggests the possibility of a neural reflex mechanism. Preliminary reports have noted similar findings in patients with nasal allergy and no history of asthma.⁴⁶

Mouth breathing caused by nasal obstruction

Nasal blockage resulting from tissue swelling and retained secretions may cause a shift from the normal pattern of nasal breathing to predominantly mouth breathing. Previous work has shown that mouth breathing associated with nasal obstruction increased the intensity of exercise-induced bronchospasm, whereas nasal breathing reduced asthma after exercise.⁴⁷ Improvements in asthma associated with nasal breathing may be the result of superior humidification and warming of inspired air before it reaches the lower airways.⁴⁸ It also is expected that airborne allergens and pollutants would be less likely to enter the lungs during periods of normal nasal function. However, a small study involving patients allergic to cats showed that complete nasal occlusion with nose clips did not enhance the asthmatic response to cat-room challenge.⁴⁹ Larger studies are needed to confirm these preliminary findings.

Pulmonary aspiration of nasal contents

Galen noted an association between nasal disease and asthma and postulated that secretions dripped from the skull into the lungs. Studies from the 1920s and 1930s suggested that substances placed in the upper respiratory tract were recoverable later from the tracheobronchial tree.^{50, 51} Huxley et al in 1978 investigated pharyn-

geal aspiration during sleep among both healthy persons and in patients with depressed sensorium.⁵² With a radiolabeled marker that was intermittently released into the nose, pulmonary aspiration was detected in a substantial number of both healthy and ill persons. Bardin et al., however, were unable to document marked aspiration of radionuclide in a study involving 13 patients with chronic rhinosinusitis and asthma.⁵³

To help define the relation between upper airway inflammation and asthma, Brugman et al. performed a series of experiments using a rabbit model of rhinosinusitis and lower airway responsiveness.⁵⁴ After inducing granulocytic rhinosinusitis, with the use of complement component C5a des arg, lung mechanics and bronchial reactivity to inhaled histamine were measured. Although there were no changes in baseline pulmonary function, histamine responsiveness increased with the presence of upper airway inflammation. These changes in reactivity were blocked by strategies that prevented the exudate from draining beyond the larynx. Observations from this animal model suggest that upper airway inflammation augments nonspecific bronchial responsiveness by means of aspiration of nasal drainage. My coworkers and I examined the pathogenic role of granulocytes in inducing airway responsiveness in this animal model.⁵⁵ Rabbits were first treated with intravenous nitrogen mustard to deplete granulocytes from the systemic circulation. After injection of the maxillary sinuses with C5a des arg, neutrophils and eosinophils were notably absent from the nasal-sinus exudate, and bronchial responsiveness was unchanged. Granulocytes, therefore, appear to be required for the changes in reactivity in this model. Combining these experimental findings with those of prior studies of pharyngeal aspiration in human subjects, it can be speculated that postnasal drainage of inflammatory cells during sleep may affect lower airway responsiveness.

It is difficult to determine which of these experimental mechanisms is most important in linking the nose to the lower airways. In all likelihood, all three phenomena contribute in some way to alterations in lung function in patients with allergic rhinitis and asthma.

SUMMARY AND FUTURE DIRECTIONS

Epidemiologic surveys have shown that allergic rhinitis and asthma commonly coexist and that an important minority of patients with nasal allergy demonstrate nonspecific bronchial hyperresponsiveness in the absence of overt asthma. A limited number of studies suggest that allergic rhinitis is a risk factor for asthma and that asymptomatic bronchial hyperresponsiveness may influence this process. Among patients who have both rhinitis and asthma, intranasal corticosteroids and antihistamines, with or without decongestants, reduce asthma symptoms and in some instances improve pulmonary function and bronchial hyperresponsiveness. Although pathophysiologic connections between the nose and lungs are not entirely understood, laboratory studies with both animal and human subjects suggest

that a nasal-bronchial reflex, shifts in breathing patterns, and pulmonary aspiration of nasal contents may contribute to lower airway dysfunction among patients with rhinitis.

Although treatment of allergic rhinitis appears to have beneficial effects on concomitant asthma, it is unclear whether nasal therapy can alter the natural history of respiratory allergy. Long-term controlled studies with rhinitis therapy or allergy immunotherapy will be of great importance in determining whether the development of asthma can be prevented among patients with rhinitis alone.

REFERENCES

1. Blair H. Natural history of childhood asthma: 20-year follow-up. *Arch Dis Child* 1977;52:613-9.
2. Smith JM. Epidemiology and natural history of asthma, allergic rhinitis and atopic dermatitis (eczema). In: Middleton E, editor. *Allergy: principles and practice*. St. Louis: Mosby, 1988:891-929.
3. Pedersen PA, Weeke ER. Asthma and allergic rhinitis in the same patients. *Allergy* 1983;38:25-9.
4. Settipane GA. Allergic rhinitis: update. *Otolaryngol Head Neck Surg* 1986;94:470-5.
5. Evans R III, Mullally DI, Wilson RW, et al. National trends in the morbidity and mortality of asthma in the U.S.: prevalence, hospitalization and death from asthma over two decades, 1965-1984. *Chest* 1987;91:65S-74S.
6. Broder I, Higgins MW, Mathews KP, Keller JB. Epidemiology of asthma and allergic rhinitis in a total community, Tecumseh, Michigan. *J Allergy Clin Immunol* 1974;54:100-10.
7. Van Arsdel PP Jr, Motulsky AG. Frequency and heritability of asthma and allergic rhinitis in college students. *Acta Genet* 1959;9:101-14.
8. Maternowski CJ, Mathews KP. The prevalence of ragweed pollinosis in foreign and native students at a midwestern university and its implications concerning methods for determining inheritance of atopy. *J Allergy* 1962;33:130-40.
9. Settipane RJ, Hagy GW, Settipane GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Proc* 1994;15:21-5.
10. Townley RG, Dennis M, Itkin IH. Comparative action of acetyl-beta-methylcholine, histamine, and pollen antigens in subjects with hay fever and patients with bronchial asthma. *J Allergy* 1965;36:121-37.
11. Madonini E, Briatico-Vangosa G, Pappacoda A, Maccagni G, Cardani A, Saporiti F. Seasonal increase of bronchial reactivity in allergic rhinitis. *J Allergy Clin Immunol* 1987;79:358-63.
12. Ramsdale EH, Morris MM, Robers RS, Hargreave FE. Asymptomatic bronchial hyperresponsiveness in rhinitis. *J Allergy Clin Immunol* 1985;75:573-7.
13. Townley RG, Ryo UY, Kolotkin B, Kang B. Bronchial sensitivity to methacholine in current and former asthmatic and allergic rhinitis and control subjects. *J Allergy Clin Immunol* 1975;56:429-42.
14. Verdiani P, Di Carlo S, Baronti A. Different prevalence and degree of nonspecific bronchial hyperreactivity between seasonal and perennial rhinitis. *J Allergy Clin Immunol* 1990;86:576-82.
15. Braman SS, Barrows AA, De Cotis BA, et al. Airway hyperresponsiveness in allergic rhinitis: a risk factor for asthma. *Chest* 1987;91:671-4.
16. Prieto L, Berto JM, Gutierrez V. Airway responsiveness to methacholine and risk of asthma in patients with allergic rhinitis. *Ann Allergy* 1994;72:534-9.
17. Corren J, Adinoff AD, Buchmeier AD, Irvin CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992;90:250-6.
18. Watson WTA, Becker AB, Simons FER. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma:

- effect on lower airway responsiveness. *J Allergy Clin Immunol* 1993;91:97-101.
19. Welsh PW, Stricker WE, Chu C-P, et al. Efficacy of beclomethasone nasal solution, flunisolide and cromolyn in relieving symptoms of ragweed allergy. *Mayo Clin Proc* 1987;62:125-34.
 20. Henriksen JW, Wenzel A. Effect of an intranasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing and asthma. *Am Rev Respir Dis* 1984;130:1014-8.
 21. Aubier M, Clerici C, Neukirch F, Herman D. Different effects of nasal and bronchial glucocorticosteroid administration on bronchial hyperresponsiveness in patients with allergic rhinitis. *Am Rev Respir Dis* 1992;146:122-6.
 22. Casale TB, Wood D, Richerson HB, et al. Elevated bronchoalveolar lavage fluid histamine levels in allergic asthmatics are associated with methacholine bronchial hyperresponsiveness. *J Clin Invest* 1987;79:1197-1203.
 23. Bousquet J, Godard FBM. Antihistamines in the treatment of asthma. *Eur Respir J* 1992;5:1137-42.
 24. Taytard A, Beaumont D, Pujet JC, Sapene M, Lewis PJ. Treatment of bronchial asthma with terfenadine: a randomized controlled trial. *Br J Clin Pharmacol* 1987;24:743-6.
 25. Rafferty P, Jackson L, Smith R, Holgate ST. Terfenadine, a potent H₁-receptor antagonist in the treatment of grass pollen sensitive asthma. *Br J Clin Pharmacol* 1990;30:229-35.
 26. Wood-Baker R, Smith R, Holgate ST. A double-blind, placebo controlled study of the effect of the specific histamine H₁-antagonist, terfenadine, in chronic severe asthma. *Br J Clin Pharmacol* 1995;39: 671-5.
 27. Bruttman G, Pedraia P, Arendt C, Rihoux JP. Protective effect of cetirizine in patients suffering from pollen asthma. *Ann Allergy* 1990;64:224-8.
 28. Dijkman JH, Hekking PRM, Molkenboer JF, et al. Prophylactic treatment of grass pollen-induced asthma with cetirizine. *Clin Exp Allergy* 1990;20:483-90.
 29. Grant JA, Nicodemus CF, Findlay SR, et al. Cetirizine in patients with seasonal allergic rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 1995; 95:923-32.
 30. Karlin JM. The use of antihistamines in asthma. *Ann Allergy* 1972;30:342-7.
 31. Corren J, Harris A, Fournier J, et al. Efficacy and safety of Claritin-D in patients with seasonal allergic rhinitis (SAR) and asthma. *Ann Allergy Asthma Immunol*. In press.
 32. Sluder G. Asthma as a nasal reflex. *JAMA* 1919;73:589-91.
 33. Whicker JH, Kern EB. The nasopulmonary reflex in the awake animal. *Ann Otol Rhinol Laryngol* 1973;82:355-8.
 34. Tomori Z, Widdicombe JG. Muscular, bronchomotor, and cardiovascular reflexes elicited by mechanical stimulation of the respiratory tract. *J Physiol* 1969;200:25-49.
 35. Nadel JA, Widdicombe JG. Reflex effects of upper airway irritation on total lung resistance and blood pressure. *J Appl Physiol* 1962;17: 861-5.
 36. Kaufman J, Wright GW. The effect of nasal and nasopharyngeal irritation on airway resistance in man. *Am Rev Respir Dis* 1969;100: 626-30.
 37. Kaufman J, Chen JC, Wright GW. The effect of trigeminal resection on reflex bronchoconstriction after nasal and nasopharyngeal irritation in man. *Am Rev Respir Dis* 1970;101:768-9.
 38. Wyllie JW, Kern EB, O'Brien PC, Hyatt RE. Alteration of pulmonary function associated with artificial nasal obstruction. *Surg Forum* 1976;27:535-7.
 39. Nolte D, Berger D. On vagal bronchoconstriction in asthmatic patients by nasal irritation. *Eur J Respir Dis* 1983;64(Suppl):110-4.
 40. Yan K, Salome C. The response of the airways to nasal stimulation in asthmatics with rhinitis. *Eur J Respir Dis* 1983;64(Suppl):105-8.
 41. Hoehne JH, Reed CE. Where is the allergic reaction in ragweed asthma? *J Allergy Clin Immunol* 1971;48:36-9.
 42. Schumacher MJ, Cota KA, Taussig LM. Pulmonary response to nasal-challenge testing of atopic subjects with stable asthma. *J Allergy Clin Immunol* 1986;78:30-5.
 43. Littell NT, Carlisle CC, Millman RP, Braman SS. Changes in airway resistance following nasal provocation. *Am Rev Respir Dis* 1990; 141:580-3.
 44. Small P, Biskin N. The effects of allergen-induced nasal provocation on pulmonary function in patients with perennial allergic rhinitis. *Am J Rhinol* 1989;3:17-20.
 45. Corren J, Adinoff AD, Irvin CG. Changes in bronchial responsiveness following nasal provocation with allergen. *J Allergy Clin Immunol* 1992;89:611-8.
 46. Plotkowski LM, Dessanges TF, Larand F, et al. Nasal pollen challenge causes bronchial hyperresponsiveness to methacholine in patients with allergic rhinitis [abstract]. *Am Rev Respir Dis* 1990; 141:A652.
 47. Shturman-Ellstein R, Zeballos RJ, Buckley JM, Souhara JF. The beneficial effect of nasal breathing on exercise-induced bronchoconstriction. *Am Rev Respir Dis* 1978;118:65-73.
 48. Griffin MP, McFadden ER, Ingram RH. Airway cooling in asthmatic and nonasthmatic subjects during nasal and oral breathing. *J Allergy Clin Immunol* 1982;69:354-9.
 49. Wood RA, Eggleston PA. The effects of intranasal steroids on nasal and pulmonary responses to cat exposure. *Am J Respir Crit Care Med* 1995;151:315-20.
 50. Mullen WV, Wyder CT. Experimental lesions of lungs produced by the inhalation of fluid from the nose and throat. *Am Rev Tuberc* 1920;4:683-7.
 51. McLaurin JG. Chest complications of sinus disease. *Ann Otol Rhinol Laryngol* 1932;41:780-93.
 52. Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspiration in normal adults and patients with depressed consciousness. *Am J Med* 1978;64:564-8.
 53. Bardin PG, Van Heerden BB, Joubert JR. Absence of pulmonary aspiration of sinus contents in patients with asthma and sinusitis. *J Allergy Clin Immunol* 1990;86:82-8.
 54. Brugman SM, Larsen GL, Henson PM, Honor J, Irvin CG. Increased lower airways responsiveness associated with sinusitis in a rabbit model. *Am Rev Respir Dis* 1993;147:314-20.
 55. Corren J, Honor J, Irvin CG. Activated neutrophils are crucial for development of bronchial hyperresponsiveness in sinusitis [abstract]. *Am Rev Respir Dis* 1990;141:A177.