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Introduction

The relationship between the uppermost airways (which consist of the two nasal passages and the paranasal sinuses) and the lower airways (the bronchi and bronchioles) is of great interest both from clinical and physiologic standpoints. To understand illnesses which, on the surface, appear to affect only one element of an integral organ system, one should be able to understand and to visualize the function of the entire system. This will allow us to examine whether such illnesses impact various other elements of this system and, conversely, whether they are influenced by the function (or dysfunction) of these elements. The therapeutic implications of this approach are obvious.

Several respiratory illnesses affect the nose and the lower airways concomitantly. These include very common disorders, such as the short-lasting common cold, as well as chronic conditions, such as cystic fibrosis. One of the goals of this report is to present evidence supporting the concept that allergic airways disease follows the same paradigm. The second goal is to discuss possible mechanisms through which dysfunction of the uppermost airways may affect the lower airways. Some of these mechanisms are not unique for allergic airways disease.

A model for chronic allergic airway disease

In the course of the past few years, we have proposed the model which is graphically depicted in Fig. 1 to describe chronic allergic airways disease as a single entity that includes rhinosinusitis and asthma. According to this model, allergic airways disease has a wide spectrum of

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severity, the gradations of which form a continuum. At the mildest end lies mild upper airways disease, whereas the severe end is occupied by severe rhinosinusitis associated with asthma. Somewhere in the middle, one can envision cases of moderate to severe rhinitis or rhinosinusitis which are accompanied by lower airways hyperresponsiveness in the absence of any asthma symptomatology. A central concept behind this model is that, because of anatomic reasons, the upper airways constitute the first target for allergens and for physical and chemical environmental stimuli; therefore, they tend to be the first to be affected by allergic airways disease and, if the intensity of this disease is low, the upper airways may be the only part of the respiratory tract that is affected. A second concept is that, when the entire respiratory tract is involved in the allergic airways disease syndrome, rhinosinusitis and asthma follow a parallel course.

Several postulates derive from the above aspects of the model. These are presented in Table 1. In order to test the validity of the model, these postulates need to be proven true. Unfortunately, systematic research in this field has not been performed and, therefore, the evidence supporting these postulates is scarce. The existing evidence, however, which will be presented below, indicates that the model has merit.

Another central concept of this model is that the upper airways influence the function of the lower airways and that this is particularly evident and relevant in allergic airways disease. This concept is supported by studies examining the effects of manipulations of the upper airways on the function of the lower airways in health and disease and on therapeutic trials in which treatment of the upper airways disease results in both symptomatic and functional improvement of the lower airways disease. The therapeutic trials are reviewed in detail elsewhere in this issue.

The coexistence and parallel relationship of allergic rhinitis and asthma

Postulate 1: rhinitis should be ubiquitous in allergic asthma

At first glance, the existing literature does not seem to support this hypothesis. In several reports the prevalence of rhinitis in asthma ranges between 28 and 85% (1–7). Unfortunately, the epidemiologic work in this field is poor. To begin with, there is no agreement as to the definition of rhinitis which, given the lack of standardized and acceptable objective indices, relies on reported sympto-

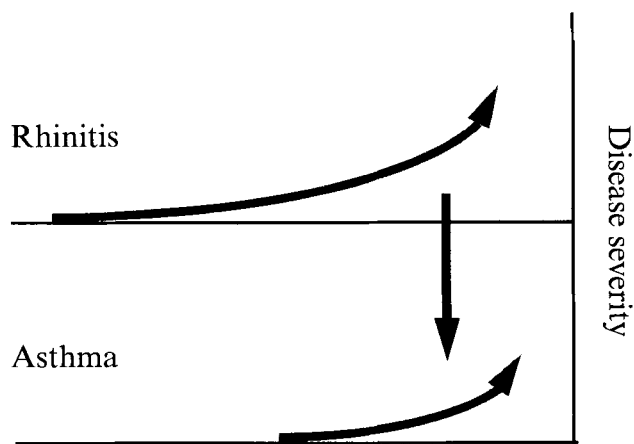


Figure 1. A schematic model to explain the relationship between rhinitis and asthma. If these two entities were regarded as the manifestations of a chronic allergic airway inflammatory disease in two different parts of the respiratory system, and if one envisions this cartoon as representative of a cross-sectional analysis of patients falling into various severity strata of the single chronic allergic airway disease, individuals with the mildest form of the syndrome would be placed at the left part of the graph and would only present with mild to moderate upper airway disease. On the other hand, individuals with the most severe manifestation of chronic allergic airway inflammatory disease would belong to the rightmost part of the graph. In addition to this “parallel” relationship between rhinitis and asthma, this model proposes an interaction stemming from the upper and affecting the lower airways.

matology alone. Secondly, most published data derive from small populations of patients whose diagnosis of asthma is not necessarily well documented and the questions posed to them (such as, “do you have allergic rhinitis?”, “do you have hay fever?” or “do you experience problems with your nose?”) are not sensitive enough, especially in patients who have sought medical attention for their asthma and are, therefore, preoccupied with their lower airways symptoms.

Recently, we documented that the prevalence of rhinitis in patients with asthma of allergic etiology is in the 90% range (8). In three different groups of well-characterized asthmatics with at least one positive epicutaneous immediate hypersensitivity skin test totaling approximately 650 and including adults, adolescents and children, the diagnosis of rhinitis was assigned if they reported a seasonal or year-round presence of at least two upper airways symptoms, in the absence of a cold or, flu. The list of probed symptoms included sneezing, nasal congestion, rhinorrhea and posterior nasal drainage. Interestingly, in a much smaller number of asthmatic individuals with a totally negative skin test panel (nonallergic), the prevalence of rhinitis was lower, around 75%. In other recent studies, including one of patients with occupational asthma (9), the prevalence of

Table 1. Postulates deriving from the model of association between rhinitis and asthma presented in Fig. 1. Epidemiologic and experimental evidence supporting these postulates is described in the text

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- Rhinitis should be ubiquitous in allergic asthma
 - Allergic rhinitis should be a predisposing factor for asthma
 - Individuals with asthma and rhinitis should have worse upper airways disease compared to individuals with rhinitis alone
 - Among asthmatics with allergic rhinitis, those with worse upper airways disease should have worse asthma compared to those with milder upper airway disease
-

rhinitis in asthmatics has been reported to be close to the one we have observed (7).

The question is raised as to what may be different in the remaining 10–15% of patients with asthma who deny any symptoms from the upper respiratory tract. Interesting information concerning such patients derives from the work of Gaga and colleagues, who have recently performed nasal mucosal biopsies in such patients as well as in patients with asthma and rhinitis and in healthy controls. These investigators found that elements of inflammation exist in the nasal mucosa of nonrhinitic asthmatics, some of which (such as the number of activated, EG2+ eosinophils) do not differentiate them from patients with asthma and rhinitis (10). Thus, even patients with asthma who do not complain of rhinitis symptoms may have histologic evidence of upper airways inflammation.

Postulate 2: allergic rhinitis should be a predisposing factor for asthma

Various studies have supported this concept. In our survey, approximately 80% of patients with asthma and rhinitis developed upper airway disease either before or at the same time as their asthma (8). In a study by Settiple and colleagues, approximately 700 college freshmen who were surveyed for the presence of asthma and allergic rhinitis were re-evaluated in a second survey 23 years later. Of those who did not have asthma in the first evaluation, but did have allergic rhinitis, 10.5% had developed asthma by the second evaluation. In contrast, among those who were originally free of rhinitis, only 3.6% had developed asthma. In other words, the odds ratio for developing asthma, if rhinitis is a pre-existing condition, is approximately 3 (11). Several other longitudinal, prospective studies have produced similar results (12, 13).

Postulate 3: individuals with asthma and rhinitis should have worse upper airway disease compared to individuals with rhinitis alone

Our group has recently generated data from various studies providing support to this postulate. First, by analyzing our

volunteer database that contains approximately 330 fully characterized individuals with asthma and rhinitis as well as 110 individuals with rhinitis alone, we have found that the percentage complaining of nasal symptoms upon exposure to various allergens and irritants is consistently higher among those with both upper and lower airways disease (14). Secondly, in the experimental setting, comparison of a group of asthmatics with rhinitis to a group with rhinitis alone, in terms of nasal responsiveness to cold, dry air, has yielded clear evidence that the former group mounts a stronger reaction to this nonantigenic stimulus, both with respect to nasal symptomatology as well as with respect to biochemical markers of mast cell and glandular activation in nasal lavage fluids (15). Support for the same concept derives from a group of patients with refractory rhinosinusitis who are being studied at the Johns Hopkins Asthma and Allergy Center in order to characterize the nature of their upper airways disease. Interestingly, without any identifiable recruitment element that could bias the sample, 50% of these patients report a history of asthma. This is higher than the prevalence of asthma in the general population (around 6%) or in nonselected populations of patients with allergic rhinitis (13–38%) (2, 3, 5, 16). Cytologic analysis of baseline nasal lavage fluids in subjects with refractory rhinosinusitis demonstrated that asthmatics have approximately four times the number of cells in their nasal fluids compared to patients with rhinosinusitis alone. This ratio is consistent if particular inflammatory cells, such as neutrophils and eosinophils, are considered (17). In addition those patients with a history of asthma, compared to those who deny lower airways symptoms, have worse olfactory ability, as measured by the University of Pennsylvania Smell Identification Test (UPSIT) (18), and have higher reported prevalence of nasal polyposis and a higher number of previous sinus surgeries.

Postulate 4: among asthmatics with allergic rhinitis, those with worse upper airways disease should have worse asthma, compared to those with milder upper airways disease

Once again, this postulate is supported by several studies, mostly of epidemiologic and/or pharmaco-economic nature

(19–21). These are cross-sectional surveys and, although they provide strong evidence for the concept, they do not offer information regarding the validity of the model on individual patients. In other words, it is not known whether the natural fluctuations of upper and lower airways disease occur in parallel. Such information can only be obtained in a prospective cohort trial which is yet to be performed.

In a study by Huse and colleagues, well-defined outcomes which are indicative of asthma severity were compared between two groups of asthmatics: those with severe allergic rhinitis and those with mild or no upper airways disease (20). In this study, which included approximately 1300 patients, the presence of severe rhinitis was associated with higher asthma morbidity. Similar data were generated by the same group in a pediatric population (19).

In 1995, we performed a retrospective survey to calculate asthma-related costs in a large database of a northeastern US health insurance company. Using standard diagnostic codes, we identified approximately 35 000 patients with asthma, of whom approximately 45% also carried the diagnosis of allergic rhinitis. This relatively low prevalence of rhinitis, as opposed to its almost ubiquitous presence in atopic asthmatics which, as mentioned above, can be demonstrated when specific rhinitis questionnaires are used (8), probably reflects the low sensitivity towards this condition by physicians who are presented with a lower airways problem and the failure of patients to seek attention for their upper airways symptoms because of their preoccupation with their asthma. Consequently, we believe that for rhinitis to be added by physicians to the list of diagnostic codes in patients with the primary complaint of asthma, the problem of the upper airways must be severe. In our study, the annual health care costs including outpatient visits, hospitalizations, as well as asthma and rhinitis medications were almost double for patients with asthma and rhinitis, in comparison to those with an asthma diagnostic code alone (21). This difference was not due only to increased medication costs but also to increased outpatient visits, and was evident in all subpopulations, including pediatric patients. The most significant finding, however, was that the difference in total medication-associated costs was due not only to the prescriptions for anti-rhinitis drugs but also to increased prescriptions for anti-asthma agents in the patients with asthma and rhinitis, in comparison to the patients with the diagnosis of asthma alone (Table 2). Although the increased prescription rates and usage of medications for asthma may not be the best indices of asthma severity, they are certainly very suggestive of

increased problems from the lower respiratory tract requiring more vigorous pharmacologic intervention.

The vertical relationship of allergic rhinitis and asthma

The clinical and experimental information presented above indicates that allergic rhinitis and asthma are, indeed, manifestations of a single nosologic entity, that of chronic allergic airways disease in the mildest forms of which only the upper airways are affected. In some of these studies, however, the findings also raise the possibility that the affliction of the upper airways *per se* has pathophysiologic impact on that of the lower airways. This possibility is indicated in Fig. 1 by the downward arrow from upper to lower airways disease. If this aspect of the chronic allergic airways disease model is correct, two additional postulates should prove true: first, experimental provocations targeting the upper airways should also adversely affect the lower airways; secondly, local treatment of rhinitis should benefit the clinical course of asthma.

Nasal provocation: effects on the lower airways

Nasal allergen challenge has both acute (within minutes) and subacute (within hours) local effects which were well described over a decade ago (22–25). In these studies, however, the lower airways were never considered. In 1971 Hoehne and Reed applied ragweed pollen grains into the noses of eight asthmatics and failed to demonstrate any acute effects on FEV₁ (26). In 1986 Schumacher and colleagues, using additional, more sensitive pulmonary function tests, also yielded relatively negative results (27). A few years later Plotkowski et al., Corren and colleagues, as well as our group, confirmed these negative findings (28–30). However, both Corren and ourselves concentrated on potential late effects on the lower airways following nasal allergen challenge. In these studies, evidence was generated that nasal allergen provocation can produce late reductions in lower airway caliber and can increase airways responsiveness in asthmatics with allergic rhinitis.

In the study published by Corren et al. in 1992, participants were selected on the basis that they reported worsening of asthma symptoms following seasonal exacerbations of their rhinitis (29). After a baseline bronchial methacholine provocation at 0800 h, liquid extract from allergenic material (or its vehicle alone) was administered to the nasal cavities through a metered pump spray around

Table 2. Percentages of patients using various anti-asthma medications. The data derive from the database of a large health insurance company of the Northwest United States

Rates of prescription medication use <i>n</i> =	Patients without the diagnosis of rhinitis 18 172	Patients with the diagnosis of rhinitis 16 176
Using inhaled β agonists	48.4	59.3
Using inhaled steroids	22.1	37.5
Using oral steroids	6.7	10.1
Using cromolyn/nedocromil	13.7	19.1
Using theophylline	15.4	19.5

1100 h. Bronchial methacholine provocation was repeated 1 and 5 h later. Following the nasal provocation with the vehicle, these investigators observed an improvement in airways responsiveness to methacholine, i.e. higher doses of the spasmogen were required to induce the targeted 20% reduction in lung function. This improvement was evident at both the 1200 h and the 1600 h timepoints and was essentially eliminated on the day of nasal allergen challenge. The inhibition of the diurnal improvement in airways responsiveness constituted indirect evidence that airways responsiveness actually increased following nasal allergen provocation. Corren and colleagues did not observe reductions in lung function during the timepoints when responsiveness appeared to have been affected by allergen challenge. Importantly, these investigators performed a control experiment using radiolabelled nasal aerosol and found that none of the solution delivered to the nose in the course of the allergen (or vehicle) provocation could be detected in the lower airways. This experiment ensured that the nasal allergen provocation was, indeed, a local event and indicated that the observed effects on the lower airways were related to the events in the nasal passages.

In a group of 15 individuals with chronic allergic airways disease who were not selected for any particular characteristic other than positive skin tests to ragweed or grasses, we replicated Corren’s protocol with some modifications (30). In this study, in order to put the effects of nasal allergen challenge on the lower airways into perspective, in addition to the nasal challenges we included two more provocations, with vehicle or allergen, this time in the lower airways. In the nasal challenge protocols, bronchial methacholine provocations were performed at baseline and at 5, 12 and 22 h after the nasal challenge. In the bronchial allergen (or vehicle) challenge protocols, methacholine provocation was performed at baseline and at 22 h after the allergen (or vehicle) challenge. Although 25–30% of the subjects participating in this study showed meaningful increases in airways responsiveness following nasal allergen provocation

(Fig. 2), the group data did not yield statistically significant changes at any timepoint. However, in this group of unselected asthmatics, neither did the inhalation of allergen to the lower airways result in significant changes in lung function or in increased airways responsiveness to methacholine. Some additional findings are noteworthy: first, in those subjects whose airways responsiveness to methacholine increased following the nasal allergen provocation, reductions in lung function were observed and these were strongly correlated with the changes in airways responsiveness; secondly, our data suggested that the asthmatics whose airways responsiveness and lung function were affected by the nasal allergen provocation were those who experienced similar changes when allergen provocation was performed on their lower airways.

Based on the last observation, a second study was designed to examine whether the patients with asthma, who experience significant changes in methacholine responsiveness and in airways function following exposure to allergen challenge, do so regardless of whether the allergen is inhaled directly into the lower airways or administered into the nose. In that study, 10 asthmatics were selected on the basis of experiencing an at least 0.33 log decrease in methacholine PD₂₀, 24 h after bronchial allergen inhalation challenge, on two consecutive occasions. Approximately 45 asthmatics had to be screened to obtain this well-defined group. Thereafter, a nasal provocation with allergen was performed and airways responsiveness was monitored 6 and 22 h later. In this group, 6 h after the nasal allergen provocation, a statistically significant increase in lower airways responsiveness to methacholine was observed (unpublished data). However, lung function was not reduced from baseline at the same timepoint. Airways responsiveness returned to baseline within 24 h.

In another trial performed by our group, asthmatics were selected on the basis of having demonstrated an inflammatory infiltrate in nasal lavage fluids between 4 and 24 h after nasal allergen challenge. In these individuals, the effects of

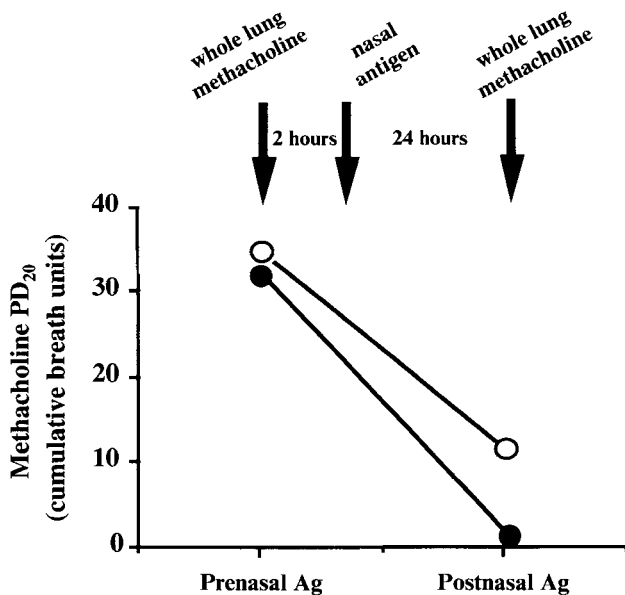


Figure 2. Example of the effect of nasal allergen provocation on lower airways responsiveness to methacholine. The data depicted derive from a single subject who underwent the experimental protocol twice within a period of 1 month, to ensure reproducibility. In both instances, significant increases in lower airways responsiveness were observed 24 h after nasal allergen challenge. In our hands, 25–30% of mild asthmatics develop increased lower airways responsiveness after nasal allergen challenge. Ag: antigen.

nasal allergen challenge on lung function and airways responsiveness to methacholine were evaluated and a pharmacologic intervention was attempted: in a double-blind, cross-over fashion, subjects were treated with an antihistamine, cetirizine, 20 mg per day for 7 days, or with placebo. As in our first trial, during the placebo arm of this study we did not observe increased methacholine responsiveness at 6 or 24 h after the nasal allergen challenge; however, once again 30% of these subjects developed increased responsiveness. In addition, FEV₁ and FVC were significantly decreased from baseline 6 h after the nasal allergen challenge, an effect that was reduced by pretreatment with cetirizine (31).

Taken together with Corren's observations, the studies presented above suggest that somewhere between 20 and 30% of patients with chronic allergic airway disease experience an interaction between the upper and the lower airways. This interaction consists of reduction in airways caliber and/or increase in airways responsiveness after nasal allergen provocation. Interestingly, these are effects that can also be observed during the same time interval, when allergen is directly inhaled into the lower airways. Moreover, evidence exists that these effects of nasal allergen challenge are more prominent in patients in whom

inhaled allergen leads to similar changes in the lower airways. The mechanism(s) behind this nose–lung interaction or behind the concordance of the physiologic effects of allergen provocation, whether it is delivered to the upper or the lower airways, is(are) unknown at this point.

Treatment of rhinitis: effects on asthma

Several studies have been performed by investigators around the globe examining the effects of rhinitis treatment on asthma. In some of these studies, systemic treatments with antihistamines or even with combination of antihistamines and decongestants were used (32–42). Because it is unknown whether these agents, in addition to their beneficial effects in rhinitis, can directly affect the lower airways, these studies cannot be used to assess the interaction between the upper and lower airways. Also, it is noteworthy that among many trials of antihistamines for the treatment of asthma, only a few have produced significant improvement in the symptoms and even fewer in lung function (32, 40, 42, 43).

The best experimental approach in this context is provided by a number of trials which have employed topical nasal corticosteroids as the treatment for rhinitis and have examined the effects of such treatment on clinical and physiologic asthma outcomes (44–49). In these trials, which are presented in more detail elsewhere in this issue, the findings have been consistent and indicative of a beneficial effect of nasal topical steroids in asthma. It is important to note that not only were asthma symptoms and medication usage reduced with nasal steroids, but lung function, airways responsiveness to methacholine and exercise-induced airway narrowing were also found to improve. Although these beneficial effects of nasal glucocorticosteroids in asthma could be partly attributable to possible, albeit very small, systemic bioavailability of these agents, it is reasonable to conclude that these findings offer further support to the overall concept that an interaction between rhinitis and asthma exists with the former contributing to the severity of the latter.

Possible mechanisms through which nasal disease may affect lower airways disease

Loss of nasal function

Galen was the first to offer insights on the function of the nose and to posit the notion that it plays a protective role for the lower airways through its ability to clean, warm and

humidify inhaled air (50). Indeed, the enormous capabilities of the nasal passages to perform these tasks are today well documented and recognized (51). In addition the nasal mucosa, through its abundant submucosal glands, provides innate immune functions through the release of antibacterials such as lysozyme and lactoferrin (52), specific immune functions by facilitating the complexing of IgA with the secretory component (53, 54) and chemical defenses, by releasing anti-oxidants such as uric acid in the epithelial lining fluid (55). Recently, it has been recognized that another product of the upper airways, mainly derived from the paranasal sinus mucosa, nitric oxide, may have very significant physiologic and protective functions for the lower human airways (56, 57).

Allergic disease may lead to partial or complete loss of the function of the nose as it pertains to its beneficial effects on the lower airways. One way by which nasal function is “lost” is when nasal airways are bypassed if complete obstruction due to mucosal congestion makes oral breathing obligatory. In such a case, the lower airways of an asthmatic patient will have to compensate for the poorer condition in which inhaled air will be when it reaches the trachea and the intrathoracic elements. A typical example of how the lower airways of patients with asthma may be affected by the bypassing of the nose derives from studies examining the effect of exercise on the lower airways when breathing takes place through the nose vs the mouth (58, 59). In these studies, exercise- or hyperventilation of air at subfreezing temperature-induced reduction in lung function was markedly attenuated when breathing took place through the nose, as opposed to the mouth.

In the setting of active allergic rhinitis breathing may, at least partially, take place through the nasal passages. Even so, the existing mucosal disease may lead to decreased ability for air-conditioning. Recently, Rouadi and colleagues examined the ability of the nasal passages to warm and humidify air and suggested that it was reduced in patients with active allergic rhinitis (60). Another possibility is that blockade of the paranasal sinus openings into the nasal cavities, as well as epithelial dysfunction resulting from chronic inflammatory sinus disease, may reduce the availability of nitric oxide in the upper and lower airways. Reduced levels of nitric oxide in nasal air samples have been reported in patients with chronic sinus disease (61) and in patients with obstructive nasal polyposis (62). However, in allergic nasal disease nasal nitric oxide levels may be higher or not different from control levels (62, 63).

Neurally mediated interaction between the nose and the lung: the nasobronchial reflex

The existence of a central reflex that originates from the sensory nerve endings, travels to the central nervous system (CNS) through the trigeminal nerve and follows an efferent pathway through the vagus nerve to produce airway smooth muscle contraction has been under debate for years. In animal models, there is little doubt that such a reflex exists (64, 65). However, the human data are controversial. In 1969, Kaufman and Wright exposed the nasal passages of healthy individuals to silica particles and observed invariable increases in tracheobronchial airway resistance. These responses were prevented by prior injection of atropine (66). One year later the same investigators reported that this phenomenon could be ablated in individuals in whom trigeminal resection had been performed to treat intractable tic douloureux (67). With trigeminal resection the sensorineural apparatus of the nose is lost. In 1983, Yan and colleagues presented their data using aerosolized nasal histamine provocations in patients with asthma, in approximately 50% of whom they found progressive reductions in lung function with increasing doses of the stimulus (68). No vehicle provocation was performed, nor was a control population of healthy subjects employed in this study, to assess whether this phenomenon is more evident in asthma. In another uncontrolled report, Nolte and Berger sprayed cold air (a freon-propelled metered dose aerosol) inside the nasal passages and produced changes in lower airway resistance in almost all subjects with asthma that they tested (69). None of their healthy controls showed any changes in resistance.

A few years later, Schumacher and colleagues used small filter paper discs applied onto the inferior turbinates, loaded with 10 µl of saline, histamine solution or allergen extract, and tested both healthy subjects and stable allergic asthmatics (27). Although most lung function parameters were not affected by any of the above provocations in any of the two subject groups, it was notable that maximal expiratory flows at 50% and 75% of vital capacity were reduced in the asthmatic group with all three nasal provocations. The authors dismissed this finding as nonspecific. However, the possibility that this “nonspecificity” is indicative of the irritant nature of the response and of the participation of the nasal sensorineural apparatus was not raised. Nevertheless Schumacher’s study, together with two subsequent publications from different groups (70, 71), “put a lid” on the debate regarding the existence of a nasobronchial reflex in humans until the recently published work by

Fontanari et al. (72, 73). These investigators performed nasal provocations with high flow bursts of cold, dry air on patients with asthma, as well as on healthy controls. Using the interruption resistance technique, they reported increased resistance in both groups during the cold air exposure, but not when warm air was used as the control provocation. Although the reported increments in airways resistance were relatively small, a number of control experiments were performed to validate the findings. Fontanari and colleagues failed to produce changes in airway resistance when the cold air was delivered into the mouth. In addition, application of lidocaine in the nasal passages reduced the effect of nasal cold air provocation on the lower airways; on the other hand, inhalation of atropine directly into the lower airways had a similar effect. We have also recently obtained experimental evidence that the nasobronchial reflex may be operable in humans. Using a potent and specific neural stimulus, capsaicin, which was aerosolized in the nose in such a way that no lower airways penetration would occur, we observed that approximately 30% of the subjects with active rhinitis and asthma demonstrated acute reductions in FEV₁ and FVC, within 30 s after the challenge. This effect was short-lasting: within a minute from the nasal provocation, the spirometric outcomes had returned to baseline. Control provocations with the capsaicin vehicle did not produce airway obstruction (unpublished observations).

Indirect support for the concept of a nasobronchial reflex can be drawn by the work of Bucca and colleagues, who have extensively evaluated a similar phenomenon relating the pharynx to the lower extrathoracic airways (74–78). In her investigations Bucca has reported that, in patients with sinusitis and asthma, or even in patients with sinusitis alone, inhalation of histamine produces extrathoracic airways obstruction evidenced by declines in the maximal inspiratory flow at 50% of vital capacity. In those individuals in whom both extra- and intrathoracic obstruction is produced by histamine inhalation, the two effects are well correlated. Interestingly, pharyngeal biopsies from patients with chronic sinusitis and extrathoracic airways “hyperresponsiveness” show evidence of increased nerve fiber density (77) offering a potential explanation for the phenomenon of extrathoracic airways obstruction being more prominent in these individuals. It is possible, therefore, that the histamine-induced extrathoracic (but also intrathoracic) airway obstruction may originate from oropharyngeal reflexes.

Even if we accept the notion that a nasobronchial reflex exists, its role in mediating the clinical consequences of the

interaction of the nose with the lower airways is not easy to envision. Based on the existing experimental evidence, this neural activity is expected to be operable only upon intense, acute stimulation of the nasal mucosa; this should occur on an episodic basis and it is doubtful that it could lead to an overall worsening of asthma. Even if we were to accept that nasal sensory nerve stimulation by the products of allergic reactions (e.g. histamine, bradykinin) or by environmental irritants takes place constantly, the unavoidable tachyphylaxis of the sensory nerves should dampen any untoward reflex effects on the lower airways. On the other hand, it is worth pointing out that, in active allergic disease of the nasal airways, the sensorineural apparatus appears to be upregulated to a state of hyperresponsiveness making it quite susceptible to stimulation by endogenous biochemical products and by exogenous irritants (79–83). The phenomenon of neural hyperresponsiveness may potentiate the nasobronchial reflex to the extent that it becomes clinically significant. This concept requires experimental support.

Propagation of inflammation from the upper to the lower airways via the airways

The concept that inflammatory product-rich secretions from the upper airways of patients with rhinosinusitis, or even with rhinitis, are aspirated into the lower airways with adverse consequences has been invoked almost as a dogma by clinicians and is widely viewed as the mechanism for lower airways symptoms, especially after an upper respiratory infection. It is quite possible that early morning coughing in individuals with acute or chronic upper airways disease is associated with accumulation of secretions in the lower pharyngeal area, stimulating irritant receptors (84). It is questionable, however, whether these secretions can reach the intrathoracic lower airways in adequate quantities to alter their physiology and to generate exacerbations, or to chronically worsen lower airway function in patients with asthma. By placing traced material in the posterior oropharynx and monitoring its appearance within the lung fields, Huxley and colleagues demonstrated several years ago, that, even individuals with intact sensorium may experience aspiration (85). However, in 1990, Bardin et al. injected traced material in the maxillary sinuses of patients with acute sinusitis and asthma but failed to detect any radioactivity within the lung fields in the next 24 h (86). The most intriguing data related to this concept derive from a rabbit model of inflammatory, sterile sinusitis induced by injection of the chemoattractive complement fragment C5a des arg into the maxillary sinuses (87). In that model, it was

demonstrated that the development of sinusitis is associated with lower airways hyperresponsiveness. Injection of the complement fragments into a knee joint, despite the induction of local inflammation, did not result in changes of airways physiology. On the other hand, the sinusitis-induced lower airways hyperresponsiveness was eliminated by positioning of the rabbits in such a way that airway secretions would not travel, by way of gravity, into the lower airways, or by eliminating upper-lower airway communication with the use of an inflated endotracheal tube cuff. This model offers strongly suggestive evidence that upper airways secretions may produce changes in lower airway physiology. Unfortunately, such experimentation would be quite difficult to reproduce in humans. Thus, with so little and conflicting evidence, the concept of upper airway secretions being the culprit behind nose–lung interaction in asthma remains elusive.

Propagation of inflammation from the upper to the lower airways via the systemic circulation

There is good evidence that allergic inflammation developing in the respiratory mucosa may result in systemic inflammatory events. For example, changes in peripheral

white blood cells, such as eosinophils, have been reported after allergen inhalation challenge of the lower airways (88–90). We also have unpublished evidence that peripheral eosinophils double in number approximately 24 h after nasal allergen challenge. Although no experimental information indicating that nasal inflammation leads to a systemic inflammatory signal that further manifests with changes in lower airways physiology exists, our current understanding of the interactions between local and systemic elements of the immune system makes this possibility worth examining.

A schematic proposal of potential pathways that may be involved in such mechanism is presented in Fig. 3. One pathway could involve absorption of spasmogens from the mucosal site of the nasal allergic reaction into the peripheral circulation. These spasmogens would then reach lower airway smooth muscle to cause bronchoconstriction. Our previously reported finding, that an antihistamine can prevent the reduction in lung function which is observed 6 h after nasal allergen challenge in patients with asthma (31), supports this pathway. However, the fact that the reduction in lung function is observed only at a later timepoint and not acutely after nasal challenge (when the highest levels of spasmogenic mediators are found in nasal

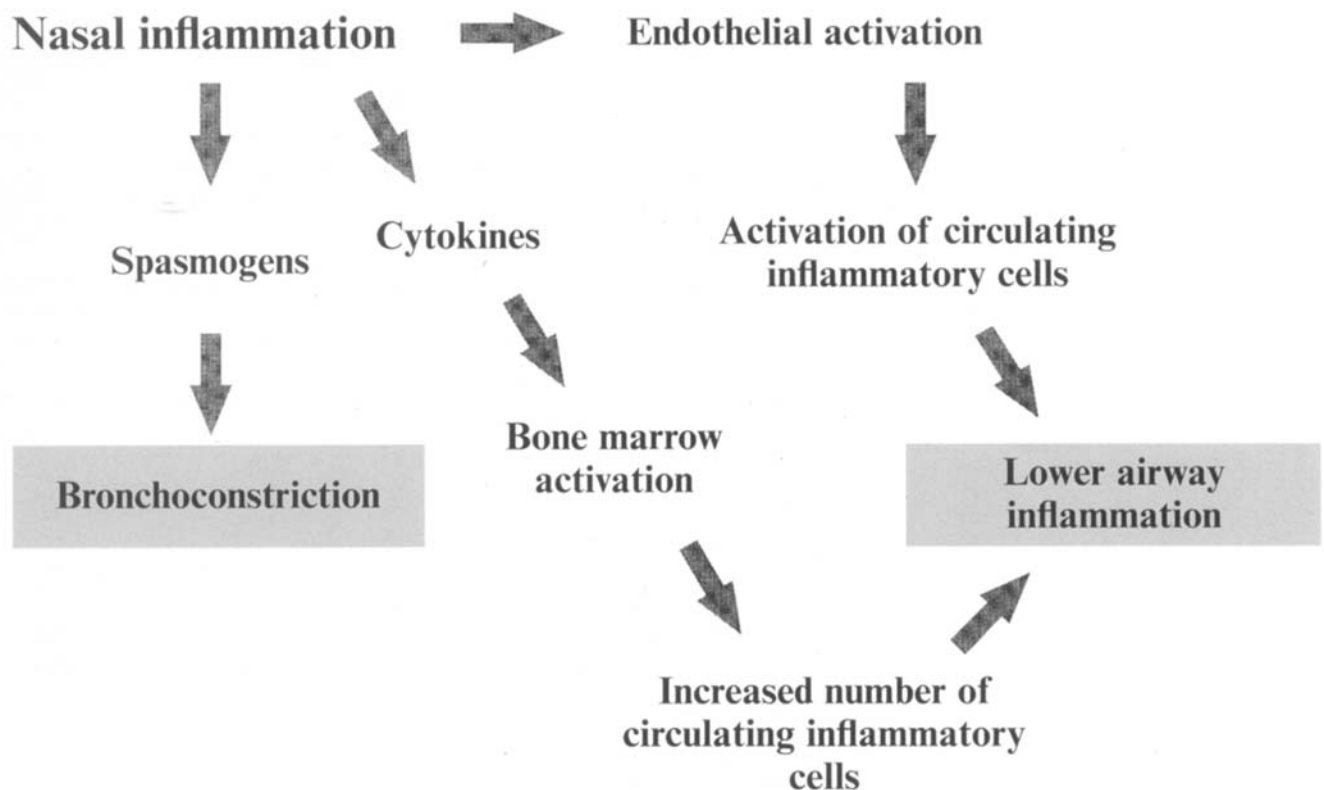


Figure 3. Potential systemic pathways through which inflammation produced by allergic reaction in the upper airways could affect the lower airways of individuals with active asthma.

lavage fluids) casts some doubts to this hypothesis. In another potential pathway, circulating inflammatory leukocytes would be activated through their interaction with adhesion molecules presented by the nasal mucosal endothelium or by cytokines released at the allergic reaction site and similarly absorbed into the blood. Activated cells would then home in tissues with ongoing inflammation which, in the case of a patient with active asthma and recently induced rhinitis, would include both the upper and lower airways mucosa. In parallel, acting as a potentiating mechanism, the same (or different) cytokines could stimulate the bone marrow to increase the number of circulating inflammatory cells. Although, as mentioned above, we have recently generated evidence of increased peripheral blood eosinophilia following nasal allergen provocation, the possibility that lower airways mucosal inflammation may increase following nasal allergen provocation has not been examined.

Conclusions

Although many unanswered questions still exist regarding the relationship between allergic rhinitis and asthma, the very rational concept that the two illnesses represent the

manifestations of a single nosologic entity in two different parts of the human respiratory tract should be entertained. In support of this concept, strong evidence that allergic rhinitis is almost ubiquitous in asthma and that the rhinitis of asthmatics may be overall more severe than that of patients with upper airways disease alone exists. In addition, the possibility that rhinitis may potentiate asthma severity is supported by the fact that asthmatics with severe rhinitis have worse asthma outcomes and use more anti-asthmatic medications to control their disease, by the experimental evidence for changes in lower airways responsiveness and caliber induced by nasal allergen challenge in 25–30% of asthmatics, and by the clinical studies indicating that treatment of rhinitis can be beneficial in asthma. The mechanisms of this interaction between the upper and the lower airways are unknown. Candidates for this role are the loss of the protective/homeostatic effects of nasal function, the activation of nasobronchial neural interactions, and the propagation of allergic inflammation from the nose to the lower airways, directly or via the systemic circulation.

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References

1. Weille FL. Studies in asthma XIX. the nose and throat in five hundred cases of asthma. *N Engl J Med* 1936;215:235–239.
2. Edfors-Lubs ML. Allergy in 7000 twin pairs. *Acta Allergol* 1971;26:249–285.
3. Peckham C, Butler NA. A national study of asthma in childhood. *J Epidemiol Commun Hlth* 1978;32:79–85.
4. Mullarkey M, Hill J, Webb D. Allergic and nonallergic rhinitis: their characterization with attention to the meaning of nasal eosinophilia. *J Allergy Clin Immunol* 1980;65:122–126.
5. Montgomery Smith J. Epidemiology and natural history of asthma, allergic rhinitis and atopic dermatitis (eczema). In: Middleton E, Reed CE, Ellis EF, editors. *Allergy, principles and practice*. St Louis: CV Mosby Co., 1983:772–803.
6. Pedersen P, Weeke E. Asthma and allergic rhinitis in the same patients. *European Journal of Allergy and Clinical Immunology* 1983;38:25–29.
7. Greisner W, Settipane R, Settipane G. Co-existence of asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Asthma Proc* 1998;19:175–179.
8. Kapsali T, Horowitz E, Togias A. Rhinitis is ubiquitous in allergic asthmatics. *J Allergy Clin Immunol* 1997;99:S138.
9. Malo J-L, Lemiere C, Desjardins A, Cartier A. Prevalence and intensity of rhinoconjunctivitis in subjects with occupational asthma. *Eur Respir J* 1997;10:1513–1515.
10. Gaga M, Lambrou D, Orphanidou H, et al. Cellular infiltration in the nasal mucosa in asthma. *Am J Respir Crit Care Med* 1998;157:A616.
11. Settipane R, Hagy G, Settipane G. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Proc* 1994;15:21–25.
12. Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence, and relationship to prior and concurrent atopic disease. *Thorax* 1992;47:537–542.
13. Jenkins MA, Hopper JL, Flander LB, Carlin JB, Giles GG. The associations between childhood asthma and atopy, and parental asthma, hay fever and smoking. *Paediatr Perinat Epidemiol* 1993;7:67–76.
14. Scichflone N, Sanico AM, Diemer FB, Horowitz E, Togias A. Symptom triggers in rhinitis and asthma (abstract). *J Allergy Clin Immunol* 1999;103:S8.
15. Stephens L, Proud D, Togias A. Nasal cold, dry air (CDA) challenge results in stronger nasal and pulmonary responses in asthmatics compared to patients with rhinitis (abstract). *J Allergy Clin Immunol* 1996;97:A315.
16. Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. *Thorax* 1991;46:895–901.
17. Sampaio F, Proud D, Leopold D, Kim J, Moylan B, Togias A. Asthmatics with rhinosinusitis have worse upper airway disease compared to patients with rhinosinusitis alone (abstract). *ACI International* 1997;Suppl. 4:136.

18. Sampaio F, Togias A, Proud D, Kim J, Moylan B, Leopold D. The presence of asthma (AS) is associated with worse olfaction in patients with chronic rhinosinusitis (CR). *Proc Int Rhinol Centennial XVI ISIAN* 1997.
19. Huse DM, Hartz SE, Russell MW, Piercey G, Weiss S. Allergic rhinitis may worsen asthma symptoms in children: the international asthma outcomes registry [abstract]. *Am J Respir Crit Care Med* 1996;**153**:A860.
20. Huse DM, Hartz SE, Klaus DH, Piercey GE, Richner R, Weiss ST. Does allergic rhinitis exacerbate asthma symptoms in adults? The asthma outcomes registry [abstract]. *Eur Respir J* 1996;**9**:351S.
21. Halpern M, Richner R, Togias A, Guo C, de Lissovoy G. Allergic rhinitis may increase asthma costs [abstract]. *Am J Respir Crit Care Med* 1996;**153**:A860.
22. Naclerio R, Meier H, Kagey-Sobotka A, Adkinson N, Meyers D, Norman P, Lichtenstein L. Mediator release after nasal airway challenge with allergen. *Am Rev Respir Dis* 1983;**128**:597–602.
23. Naclerio R, Proud D, Togias A, et al. Inflammatory mediators in late antigen-induced rhinitis. *N Engl J Med* 1985;**313**:65–70.
24. Bascom R, Pipkorn U, Lichtenstein L, Naclerio R. The influx of inflammatory cells into nasal washings during the late response to antigen challenge. Effect of steroid pretreatment. *Am Rev Respir Dis* 1988;**138**:406–412.
25. Togias A, Naclerio R, Proud D, et al. Mediator release during nasal provocation: a model to investigate the pathophysiology of rhinitis. *Am J Med* 1986;**79**(Suppl. 6A):26–33.
26. Hoehne JH, C.E R. Where is the allergic reaction in ragweed asthma? *J Allergy Clin Immunol* 1971;**48**:36–39.
27. Schumacher M, Cota K, Taussig L. Pulmonary response to nasal-challenge testing of atopic subjects with stable asthma. *J Allergy Clin Immunol* 1986;**78**:30–35.
28. Plotkowski L, Dessanges J, Lavaud F, Hanhahart F, Lockhart A. Nasal pollen challenge causes bronchial hyperresponsiveness to methacholine in patients with allergic rhinitis [abstract]. *Am Rev Respir Dis* 1990;**141**:A652.
29. Corren J, Adinoff A, Irvin C. Changes in bronchial responsiveness following nasal provocation with allergen. *J Allergy Clin Immunol* 1992;**89**:611–618.
30. Windom H, Lim-Monbay M, Thompson M, Naclerio R, Togias A. The effect of nasal versus bronchial antigens (Ag) challenge on the asthmatic airways [abstract]. *J Allergy Clin Immunol* 1992;**89**:334.
31. Noureddine G, Thompson M, Brennan F, Proud D, Kagey-Sobotka A, Lichtenstein L, Naclerio R, Togias A. Nasal antigen challenge in asthmatics: effects of ceterizine (CET) on nasal and pulmonary responses (abstract). *J Allergy Clin Immunol* 1994;**93**:177.
32. Corren J, Harris A, Aaronson D, et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. *J Allergy Clin Immunol* 1997;**100**:781–788.
33. Finnerty J, Holgate S. Evidence for the roles of histamine and prostaglandins as mediators in exercise-induced asthma: the inhibitory effect of terfenadine and flurbiprofen alone and in combination. *Eur Respir J* 1990;**3**:540–547.
34. Finney M, Anderson S, Black J. Terfenadine modifies airway narrowing induced by the inhalation of nonisotonic aerosols in subjects with asthma. *Am Rev Respir Dis* 1990;**141**:1151–1157.
35. Patel K. Terfenadine in exercise-induced asthma. *Br Med J* 1984;**285**:1496–1497.
36. Wiebicke W, Poynter A, Montgomery M, Chernick V, Pasterkamp H. Effect of terfenadine on the response to exercise and cold air in asthma. *Pediatr Pulmonol* 1988;**4**:225–229.
37. de Bruin-Weller M, Rijssenbeck-Nouwens L, de Monchy J. Lack of effect of cetirizine on early and late asthmatic response after allergen challenge. *J Allergy Clin Immunol* 1994;**94**:231–239.
38. Ghosh S, De Vos C, Patel K. Effect of cetirizine on exercise induced bronchoconstriction in patients with asthma (abstract). *Am Rev Respir Dis* 1990;**141**:A836.
39. Gong H, Tashkin D, Daupinee B, Djahed B, Wu T. Effects of oral cetirizine, a selective H₁ antagonist, on allergen- and exercise-induced bronchoconstriction in subjects with asthma. *J Allergy Clin Immunol* 1990;**85**:632–641.
40. Grant J, Nicodemus C, Findlay S, et al. Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 1995;**95**:923–932.
41. Malick A, Grant J. Antihistamines in the treatment of asthma. *Allergy (Suppl.)* 1997;**52**:55–66.
42. Van Ganse E, Kaufman L, Derde M, Yernault J, Delaunois L, Vincken W. Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. *Eur Respir J* 1997;**10**:2216–2224.
43. Spector S, Nicodemus C, Corren J, Schanker H, Rachelesky G, Katz R. Comparison of the bronchodilatory effects of cetirizine, albuterol, and both together versus placebo in patients with mild-to-moderate asthma. *J Allergy Clin Immunol* 1995;**96**:174–181.
44. Corren J, Adinoff A, Buchmeier A, Irvin C. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992;**90**:250–256.
45. Foresi A, Pelucchi A, Gherson G, Mastropaqua B, Chiapparino A, Testi R. Once daily intranasal fluticasone propionate (200 µg) reduces nasal symptoms and inflammation increase in bronchial responsiveness during the pollen season in allergic rhinitis. *J Allergy Clin Immunol* 1996;**98**:274–282.
46. Henriksen J, Wenzel A. Effect of an intranasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing, and asthma. *Am Rev Respir Dis* 1984;**130**:1014–1018.
47. Welsh P, Stricker W, Chu C, Naessens J, Reese M, Reed C, Marcoux J. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. *Mayo Clin Proc* 1987;**62**:125–134.
48. 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.
49. Wood R, Eggleston P. The effects of intranasal steroids on nasal and pulmonary responses to cat exposure. *Am J Respir Crit Care Med* 1995;**151**:315–320.
50. Galen. *On the usefulness of the parts of the body*. Ithaca: Cornell University Press, 1968.
51. Proctor D. Physiology of the upper airway. In: Fenn WO, Rahn H, editors. *Handbook of physiology. Section 3. Respiration*. Washington: American Physiological Society, 1964:309–346.
52. Raphael G, Jeney E, Baraniuk J, Kim I, Meredith S, Kaliner M. Pathophysiology of rhinitis: lactoferrin and lysozyme in nasal secretions. *J Clin Invest* 1989;**84**:1528–1535.
53. Brandtzaeg P. The role of humoral mucosal immunity in the induction and maintenance of chronic airway infections. *Am J Respir Crit Care Med* 1995;**151**:2081–2087.
54. Brandtzaeg P. Immunocompetent cells of the upper airway: functions in normal and diseased mucosa. *Eur Arch Oto-Rhino-Laryngol* 1995;**252**:S8–S21.
55. Peden D, Swiersz M, Ohkubo K, Hahn B, Emery B, Kaliner M. Nasal secretion of the ozone scavenger uric acid. *Am Rev Respir Dis* 1993;**148**:455–461.

56. Lundberg J, Rinder J, Weitzberg E, Lundberg J, Alving K. Nasally exhaled nitric oxide in humans originates mainly in the paranasal sinuses. *Acta Physiol Scand* 1994;152:431–432.
57. Lundberg J, Lundberg J, Settergren G, Alving K, Weitzberg E. Nitric oxide, produced in the upper airways, may act in an “aerocrine” fashion to enhance pulmonary oxygen uptake in humans. *Acta Physiol Scand* 1995;155:467–469.
58. Shturman-Ellstein R, Zeballos R, Buckley J, Souhrada J. The beneficial effect of nasal breathing on exercise-induced bronchoconstriction. *Am Rev Respir Dis* 1978;118:65–73.
59. Griffin M, McFadden E, Ingram R. Airway cooling in asthmatic and nonasthmatic subjects during nasal and oral breathing. *J Allergy Clin Immunol* 1982;69:354–359.
60. Rouadi P, Baroody F, Naureckas T, Abbott D, Solway J, Naclerio R. Allergic subjects have a reduced ability to warm air. *J Allergy Clin Immunol* 1998;101:S150.
61. Lindberg S, Cervin A, Runer T. Nitric oxide (NO) production in the upper airways is decreased in chronic sinusitis. *Acta Otolaryngol (Stockh)* 1997;117:113–117.
62. Arnal J-F, Flores P, Rami J, Murris-Espin M, Bremont F, Aguilla M, Serrano E, Didier A. Nasal nitric oxide concentration in paranasal sinus inflammatory diseases. *Eur Respir J* 1999;13:307–312.
63. Henriksen AH, Sue-Chu M, Holmen T, Langhammer A, Bjerner L. Exhaled and nasal NO levels in allergic rhinitis: relation to sensitization, pollen season and bronchial hyperresponsiveness. *Eur Respir J* 1999;13:301–306.
64. Rall JE, Gilbert NC, Trump R. Certain aspects of the bronchial reflexes obtained by stimulation of the nasopharynx. *J Lab Clin Med* 1945;30:953–956.
65. Whicker JH, Kern EB. The nasopulmonary reflex in the awake animal. *Ann Otol* 1973;82:355–358.
66. Kaufman J, Wright G. The effect of nasal and nasopharyngeal irritation on airway resistance in man. *Am Rev Respir Dis* 1969;100:626–630.
67. Kaufman J, Chen J, Wright G. The effect of trigeminal resection on reflex bronchoconstriction after nasal and nasopharyngeal irritation in man. *Am Rev Respir Dis* 1970;101:768–769.
68. Yan K, Salome C. The response of the airways to nasal stimulation in asthmatics with rhinitis. *Eur J Respir Dis* 1982;64(Suppl. 128):105–109.
69. Nolte D, Berger D. On vagal bronchoconstriction in asthmatic patients by nasal irritation. *Eur J Respir Dis* 1983;64:110–114.
70. Levi C, Tyler G, Olson L, Saunders N. Lack of airway response to nasal irritation in normal and asthmatic subjects. *Aust NZ J Med* 1990;20:578–582.
71. Littell N, Carlisle C, Millman R, Braman S. Changes in airway resistance following nasal provocation. *Am Rev Respir Dis* 1990;141:580–583.
72. Fontanari P, Burnet H, Zattara-Hartman M, Jammes Y. Changes in airway resistance induced by nasal inhalation of cold dry, or moist air in normal individuals. *J Appl Physiol* 1996;81:1739–1743.
73. Fontanari P, Zattara-Hartmann M-C, Burnet H, Jammes Y. Nasal eupnoic inhalation of cold, dry air increases airway resistance in asthmatic patients. *Eur Respir J* 1997;10:2250–2254.
74. Bucca C, Rolla G, Bugiani M, Olivia A, Scappaticci E, Brussino L. Accuracy of the MIF50 histamine dose-response curve to assess extrathoracic airway hyperresponsiveness [EA-HR] (abstr). *Am Rev Respir Dis* 1990;141:A730.
75. Bucca C, Rolla G, Scappaticci E, et al. Extrathoracic and intrathoracic airway responsiveness in sinusitis. *J Allergy Clin Immunol* 1995;95:52–59.
76. Bucca C, Rolla G, DeRose V, Bugiani M. Are asthma-like symptoms due to bronchial or extrathoracic airway dysfunction? *Lancet* 1995;346:791–795.
77. Rolla G, Colagrande P, Scappaticci E, et al. Damage of the pharyngeal mucosa and hyperresponsiveness of airway in sinusitis. *J Allergy Clin Immunol* 1997;100:52–57.
78. Rolla G, Colagrande PMM, Debernardi V, et al. Extrathoracic airway dysfunction in cough associated with gastroesophageal reflux. *J Allergy Clin Immunol* 1998;102:209–209.
79. Sanico A, Togias A. Neuronal dysfunction and its role in rhinitis. In: Oehling AK, Lopez JGH, editors. *Proc ICACI XVI/EAACI* 97 1997;185–190.
80. Sanico A, Lai G, Krishnan S, Togias A. Nasal hyperresponsiveness to capsaicin in active allergic rhinitis (abstract). *J Allergy Clin Immunol* 1998;101:S150.
81. Sanico A, Philip G, Proud D, Naclerio R, Togias A. Comparison of nasal mucosal responsiveness to neuronal stimulation in nonallergic and allergic rhinitis: effects of capsaicin nasal challenge. *Clin Exp Allergy* 1998;28:92–100.
82. Sanico AM, Philip G, Lai G, Togias A. Hyperosmolar saline induces reflex nasal secretions, evincing neural hyperresponsiveness in allergic rhinitis. *J Appl Physiol* 1999;86:1202–1210.
83. Sanico AM, Koliatsos VE, Stanis AM, Bienenstock J, Togias A. Neural hyperresponsiveness and nerve growth factor in allergic rhinitis. *Int Arch Allergy Immunol* 1999 (in press).
84. Carney I, Gibson P, Murree-Allen K, Saltos N, Olsson L, Hensley M. A systematic evaluation of mechanisms in chronic cough. *Am J Respir Crit Care Med* 1997;156:211–216.
85. Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspiration in normal adults and patients with depressed consciousness. *Am J Med* 1978;64:564–568.
86. Bardin P, VanHeerden B, Joubert J. Absence of pulmonary aspiration of sinus contents in patients with asthma and sinusitis. *J Allergy Clin Immunol* 1990;86:82–88.
87. Brugman S, Larsen G, Henson P, Honor J, Irvin C. Increased lower airways responsiveness associated with sinusitis in a rabbit model. *Am Rev Respir Dis* 1993;147:314–320.
88. Durham S, Carroll M, Walsh G, Kay A. Leukocyte activation in allergen-induced late-phase asthmatic reaction. *N Engl J Med* 1984;311:1398–1402.
89. Cookson W, Craddock C, Benson M, Durham S. Falls in peripheral eosinophil counts parallel the late asthmatic response. *Am Rev Respir Dis* 1989;139:458–462.
90. Durham S, Loegering D, Dunnette S, Gleich G, Kay A. Blood eosinophils and eosinophil-derived proteins in allergic asthma. *J Allergy Clin Immunol* 1989;84:931–936.