

Is Rhinosinusitis a Cause of Asthma?

Brian A. Smart

Asthma and Allergy Center, DuPage Medical Group, Glen Ellyn, IL. E-mail: Brian.Smart@Dupagemd.com.

Abstract

There is a great deal of evidence of an association between rhinosinusitis and asthma. However, it is less clear whether rhinosinusitis is a direct trigger for asthma or the two conditions are simply manifestations of a common underlying process. Evidence for a role for rhinosinusitis as a trigger for asthma includes many examples of improvement in asthma once concomitant rhinosinusitis is treated medically or surgically. Possible mechanisms for this relationship include naso-pharyngo-bronchial reflexes, postnasal drip, abnormal breathing, and the local production of inflammatory mediators that trigger pulmonary inflammation via the bone marrow. On the other hand, evidence exists that rhinosinusitis and asthma are manifestations of a common process. For example, there are similarities between the histopathological changes in the epithelium in chronic rhinosinusitis and asthma. The bone marrow may provide the link between the upper and lower airways in creating a common disease. A second possible mechanism for a common disease is response to staphylococcal enterotoxins. Although evidence exists to suggest that rhinosinusitis either triggers asthma or represents a local manifestation of a shared disorder, the key to reconciling this apparent controversy is to consider that rhinosinusitis is not just a single, uniform disease. Current evidence suggests that rhinosinusitis with neither polyps nor eosinophilic inflammation acts as a direct trigger for asthma, whereas rhinosinusitis with both polyps and eosinophilic inflammation shares underlying mechanisms with asthma. Clearly, however, there is considerable overlap between the different, complex mechanisms that link rhinosinusitis to asthma.

Index Entries

Rhinosinusitis; asthma; sinusitis; polyps; eosinophil.

Introduction

In recent years, a growing theme in the specialty of allergy and immunology has been the recognition that seemingly disparate conditions may have important influence on each other and, in fact, may simply be different manifestations of a common disease. One example of this association is the relationship between rhinosinusitis and asthma. However, this relationship is controversial. Evidence exists that rhinosinusitis directly triggers asthma by various plausible mechanisms. On the other hand, there is also evidence that rhinosinusitis and asthma are simply local manifestations of a systemic disease. This article examines the evidence and attempts to reconcile this controversy.

Mechanisms of Development of Rhinosinusitis

To begin to understand the relationship between rhinosinusitis and asthma, it is important to consider the various mechanisms that have been advanced for the development of rhinosinusitis. The "infectious rhinosinusitis" mechanism involves the development of obstruction of normal drainage through the sinus ostia. This obstruction is created by inflamed tissue in acute viral rhinosinusitis or in allergic rhinitis or by anatomical abnormalities such as polyps and severe deviation of the nasal septum. Obstructed drainage creates stasis of mucus in the paranasal sinuses, which, in turn, creates an ideal culture media for bacteria. The growth of bacteria promotes further inflammation and creates a self-perpetuating chronic process.

Conversely to infectious rhinosinusitis, the "inflammatory rhinosinusitis" mechanism states that chronic rhinosinusitis (CRS) is primarily an inflammatory process and that infection is usually secondary. Numerous investigators have reported evidence for this inflammatory process. For example, in the presence or absence of demonstrable allergy, T-helper 2 (Th2) cyto-

kines typical of an allergic response have been demonstrated in the sinus mucosa in CRS. For example, in a group of 20 allergic and 15 nonallergic children with CRS and asthma, Riccio et al. (1) showed that the allergic subjects had increased interleukin (IL)-4 and tumor necrosis factor- α , with decreased IL-12 and interferon (IFN)- γ , whereas nonallergic subjects had increased IL-4 and decreased IFN- γ .

The similarity between sinus mucosa specimens in allergic and nonallergic patients with CRS also extends to the cellular infiltrate. For example, the sinus mucosa of allergic patients with CRS contains elevated numbers of eosinophils, T-cells, and B-cells, whereas in nonallergic patients with CRS (who represent the majority of patients with CRS), there is prominent infiltration of eosinophils, but numbers of T-lymphocytes are not elevated (2). The eosinophils in the sinus mucosa may create tissue damage, such as epithelial denudation (3). Bacteria may in turn superinfect areas of damaged sinus mucosa, leading to the purulent discharge, foul breath, and other features typical of CRS (4). This inflammatory model may explain why many patients with chronic sinusitis appear to respond to extended courses of antibiotics, only to experience periodic exacerbations of their disease because the underlying disease is difficult to control. The inflammatory model may also explain why surgical treatment of CRS, which is intended to relieve obstruction, has mixed success, because the inflammatory process responsible for the obstruction is not relieved.

Because CRS may be alternatively described as a primarily infection- or inflammation-driven process, any relationship between CRS and asthma may also operate by disparate mechanisms. It is important to remember that, as sharp distinctions are artificially drawn between infection- and inflammation-driven CRS, there is considerable overlap between these two processes. For example, in a group of pediatric patients, Tosca et al. (5) showed a reduction of

inflammatory cell numbers in nasal scrapings and a reduction in levels of IL-4 in rhinosinusal lavage 1 mo after treatment with antibiotics, nasal corticosteroids, and a 10-d course of oral corticosteroids in both allergic and nonallergic patients. This finding suggests that bacterial infection in the sinuses either may help create or may help perpetuate the Th2 inflammation that has been described in CRS in both allergic and nonallergic individuals.

The Relationship Between Rhinosinusitis and Asthma

There are numerous examples of the relationship between CRS and asthma. Evidence for this relationship dates back to the 1920s and 1930s from studies that identified rhinosinusitis as a trigger for asthma (6,7). More recent examinations of this relationship include a study by Bresciani et al. (8), who reported that 100% of severe steroid-dependent asthmatics had abnormal sinus CT scans, whereas 88% of patients with mild-to-moderate asthma had abnormal sinus CT scans. A report from Finland found that in adult patients with asthma exacerbations, 87% had abnormal sinus radiographs (9). Similarly, a study from the Netherlands showed that 84% of adult patients with severe asthma had abnormalities on sinus CT (10). This relationship was also demonstrated in the pediatric population in a study that showed that 27% of pediatric patients admitted in status asthmaticus had abnormal sinus radiographs, as defined by two-thirds or greater opacification of the paranasal sinuses on sinus X-ray (11). Another recent study showed that when examined by endoscopy, about 50% of children with asthma suffer from rhinosinusitis (12). These and other examples point to the strong association between rhinosinusitis and asthma.

Although the strong association between rhinosinusitis and asthma is clearly demonstrated by the evidence cited earlier, the controversy centers around the following question: is

there a causal relationship (i.e., can rhinosinusitis trigger asthma?), or is this association an epiphenomenon (i.e., are rhinosinusitis and asthma manifestations of the same underlying disease process?)? More evidence is needed to fully answer this question, but there are numerous reports that the medical or surgical management of rhinosinusitis improves co-existing asthma. This improvement in asthma after treatment for rhinosinusitis implies a role for rhinosinusitis as a trigger for asthma (13).

Medical Management

One way to prove a possible causal relationship between rhinosinusitis and asthma is to demonstrate improvement in asthma following medical treatment of rhinosinusitis. Rachelefsky et al. (14) performed a study in pediatric patients with concomitant rhinosinusitis and asthma. Rhinosinusitis in these patients was identified with sinus radiographs, and asthma was diagnosed by the presence of 3 mo or more of respiratory symptoms such as cough and/or wheeze (during both the day and the night) as well as abnormal pulmonary function tests (14). In this study, 79% of children with asthma were able to discontinue bronchodilators after their rhinosinusitis was medically treated (14). In the same study, pulmonary function tests normalized in 67% of patients who were treated medically for sinusitis (14). Friedman et al. (15) reported similar results in a group of pediatric patients with sinusitis and asthma who received medical treatment of their sinusitis. They showed improvement in asthma symptoms in the five patients who kept symptom diary cards and improvement in pulmonary function tests in five of the seven patients measured.

Another study showed that 54% of 55 children with asthma and abnormal sinus X-rays had improvement in their asthma with antibiotics, whereas 67% improved with nasal corticosteroids (16). Richards et al. (17) showed that 12 of 15 children with asthma had asthma

exacerbations following acute sinusitis, as identified by history, physical examination, and sinus X-rays. These patients demonstrated improvement in their asthma following antibiotic treatment (17). Another group, including 18 children with moderate asthma and CRS, demonstrated significant improvement in asthma symptoms and respiratory function 1 mo after treatment with antibiotics, nasal corticosteroid, and a 10-d burst of oral steroids (18).

Additionally, another study of pediatric patients with sinusitis examined improvement of bronchial hyperresponsiveness (19). In this study, methacholine challenges were performed both before and after documented sinusitis was treated with nasal saline, antibiotics, antihistamine, or decongestant and 5 d of oral steroids (19). The patients who had opacified maxillary sinuses at entry and had normal sinus X-rays after 30 d showed a decrease in sensitivity to methacholine, whereas a control group of patients with rhinitis who received the same treatment but who had normal sinus X-rays at entry and those patients with abnormal sinus X-rays that did not improve after treatment, did not show decreased sensitivity to methacholine (19).

In a study of children with mild asthma, medical treatment of rhinosinusitis resulted in a significant decrease of bronchial hyperresponsiveness to methacholine (20). An earlier study showed a similar but less impressive outcome following medical treatment of rhinosinusitis (21). In this study, 42 children with moderate-to-severe asthma and abnormal sinus X-rays were treated with ampicillin, oral decongestants, and intranasal steroids and showed improvement in asthma symptom scores and a trend toward less bronchial hyperactivity (BHR) but no change in sinus X-rays relative to controls (21).

A group from Croatia recently reported that endosinusal treatment for CRS in patients with asthma resulted in improvement in asthma (22). In this study, 18 patients with mild-to-moderate asthma received maxillary endosinusal

treatment with dexamethasone and gentamicin for 7 d (22). Thirty days after treatment, eosinophil cationic protein and tryptase levels were decreased in both the serum and sinus lavage fluid, and forced expiratory volume after 1 s (FEV₁) and subjective sinusitis scores also improved (22). It is clear that specific medical treatment of rhinosinusitis improves asthma in patients with both rhinosinusitis and asthma.

Surgical Management

Surgical management of CRS has also been shown to result in improvement of lower airway disease. For example, in a recent study, 15 adult patients with CRS who required inhaled steroids and at least intermittent oral prednisone to control asthma showed an improvement in asthma symptoms and a decline in both total dosage of steroids and number of days of steroid use in the first year following surgery (23). Another study showed both improvement in asthma symptoms and peak expiratory flow measurements following endoscopic sinus surgery (24). In a study of 20 patients with asthma and CRS (ages 16–72 yr), functional endoscopic sinus surgery (FESS) resulted in an improvement in asthma (25). After the procedure, 70% had less frequent asthma and 65% had less severe asthma, with a 75% reduction in hospitalizations and an 81% reduction in acute care visits in the year after the surgery (25). Okayama et al. (26) provided another interesting perspective on the relationship between CRS and asthma in a study of 42 patients with CRS, 50 patients with stable asthma, 50 patients with chronic bronchitis, and 40 patients with allergic rhinitis in whom BHR was studied to methacholine. This study demonstrated that BHR in patients with CRS was less than that of patients with asthma but was similar to the BHR of patients with chronic bronchitis or allergic rhinitis (26). After endoscopic surgery for CRS, the subjects had a significant decrease in BHR along with improvement in both nasal symptoms and sinus pathology (26).

Similar improvements after FESS have been shown in pediatric patients with CRS and asthma. For example, in a study of 52 children ages 7 mo to 17 yr, there was an 89% reduction in chronic cough and a 96% decrease in asthma symptoms by retrospective interview performed an average of 21.8 mo after FESS (27). This study also showed a reduction in monthly asthma exacerbations from 6.7 to 2.5 and a 79% reduction in emergency room visits (27). In another study, Manning et al. (28) studied 14 steroid-dependent asthmatic children with chronic sinusitis. Following FESS, 11 of these children showed improvement in their asthma (28).

However, the data supporting an improvement in asthma after sinus surgery have not been entirely supportive. A study of 50 patients with asthma who had endoscopic surgery for sinusitis demonstrated that only 20% of the patients had a reduction in the amount of inhaled steroids required to control their asthma (29). However, this study also showed significant decreases in the use of oral steroids and of hospitalizations in the year following the surgery (29). In a study of 19 patients who underwent endoscopic surgery for sinusitis, Dhong et al. (30) found there were significant improvements in diurnal and nocturnal asthma symptoms and in asthma medication scores, but there were no changes in pulmonary function tests. Goldstein et al. (31) reported a study that was even less supportive of the hypothesis that asthma improves after sinus surgery. This group performed a retrospective analysis of medical records from 13 patients with asthma who underwent FESS for CRS and found no significant change in group mean asthma symptoms, the use of asthma medications, pulmonary function test results, number of emergency room visits, or number of hospitalizations (31).

Although the evidence for improvement in asthma symptoms and pulmonary function after treatment for concomitant rhinosinusitis is more robust for medical than for surgical treat-

ment, it is clear that rhinosinusitis has a tremendous influence on asthma. It is possible that some of the medical treatment used, such as oral antibiotics and oral steroids, had pulmonary effects in some of the aforementioned studies. Furthermore, the investigators cited earlier have used various means for defining rhinosinusitis and for measuring response to treatment for both rhinosinusitis and asthma. These different means have included, for rhinosinusitis, sinus X-rays, sinus CT, nasal endoscopy, biopsies of nasal and sinus mucosa, cytokine levels in sinus washes, and subjective symptom scores; and, for asthma, forced expiratory volume in 1 s, methacholine challenges, medication use patterns, and subjective symptom scores. This heterogeneity of methods can create confusion in interpreting trials done by different investigators. Nonetheless, it appears clear from the weight and variety of studies of both medical and surgical treatment of rhinosinusitis that this disease influences asthma independently of other disease processes. Numerous mechanisms for this relationship have been advanced.

Mechanisms for Causal Relationship Between Rhinosinusitis and Asthma

Because the medical treatment of rhinosinusitis results in improvement in concomitant asthma, a direct causative relationship between rhinosinusitis and asthma is an attractive idea. There are numerous hypotheses to explain how this relationship might exist (Table 1). One is that naso-pharyngo-bronchial reflexes may be involved in the association between upper and lower airways. These naso-bronchial reflexes have been demonstrated in both human and animal models following nasal stimulation with various substances, including silica particles, sulfur dioxide, cold air, mechanical irritation, and fumes (32–36). These reflexes can be blocked by anticholinergics, lidocaine, resection of neural connections, and ganglionic blockade (34–37).

Table 1
Proposed Mechanisms for Causal Relationship
Between Rhinosinusitis and Asthma

• Naso-pharyngo-bronchial reflexes • Drainage of inflammatory cells and mediators into the lungs • Inhalation of dry, cold air and environmental pollutants • Local upper respiratory inflammation leading to pulmonary inflammation

A postulated neuroanatomic pathway that may reflexively connect the paranasal sinuses to the lungs is as follows: receptors in the nose, pharynx, and, possibly, in the sinuses give rise to afferent fibers that form part of the trigeminal nerve (13). The trigeminal nerve connects in the brain stem (via the reticular formation) with the dorsal vagal nucleus, which, in turn, sends parasympathetic efferent fibers to the bronchi (via the vagus nerve) (13).

The parasympathetic nervous system plays a role in maintaining bronchial muscle tone and in mediating acute bronchospastic responses (13). For example, in a study of 106 patients with chronic sinusitis, histamine challenges to the lower airway were performed before and after medical treatment of sinusitis (38). FEV₁ was measured as an index of bronchial narrowing, and midinspiratory flow was measured as an index of extrabronchial airway narrowing. After medical treatment of sinusitis, both intra- and extrabronchial hyperreactivity decreased, with a greater and earlier reduction in extrabronchial hyperreactivity than intrabronchial hyperreactivity. Interestingly, the changes in intra- and extrabronchial reactivity were strongly associated with pharyngitis, which was diagnosed by history, physical examination, and nasal lavage. Based on these results, the authors proposed that airway hyperresponsiveness in rhinosinusitis might depend on pharyngo-bronchial reflexes, which are triggered by the drainage of inflammatory mediators and infected material from infected sinuses into the pharynx. In a later study, these authors demonstrated

damage of the pharyngeal mucosa in patients with CRS in the form of epithelial thinning and an increase in pharyngeal nerve fiber density (39). These findings support a mechanism of increased exposure of submucosal nerve endings to irritants, leading to the release of sensory neuropeptides via axon reflexes with activation of a neural arc, which in turn would result in reflex airway constriction.

Another study demonstrated that the local stimulation of irritant receptors by inflammatory mediators might have triggered bronchospasm (40). These investigators looked at the fluid obtained from maxillary sinus lavage in patients who underwent surgery for chronic sinusitis compared with the nasal lavage fluid of patients with allergic rhinitis (40). This study showed that levels of inflammatory mediators, such as leukotrienes, prostaglandin D₂, and histamine, were significantly elevated in patients with CRS and were in a range of concentration that was believed to be consistent with local inflammation and the stimulation of irritant receptors (40). Therefore, the available evidence supports a naso-pharyngo-bronchial reflex as a possible mechanism for a causal relationship between infectious CRS and asthma.

Another possible mechanism for a causal relationship between infectious CRS and asthma is postnasal drip or drainage of inflammatory cells and mediators into the lungs. These inflammatory cells and mediators then create increased airway reactivity and inflammation. This possible mechanism is controversial. In 1990, Bardin et al. (41) reported that there was no pulmonary aspiration of sinus contents in patients with concomitant asthma and sinusitis. This group showed that after placement of radionuclide into the maxillary sinuses, the radionuclide was visible over a 24-h period in the maxillary sinus, nasopharynx, esophagus, and lower gastrointestinal tract but not in the lungs (41). Conversely to this report, in 2003, another group reported pulmonary aspiration of radionuclide-labeled nasal secretions during sleep (42). This study included

one group of patients with sinusitis and asthma and a healthy control group; interestingly, there was no difference in degree of aspiration of nasal secretions between the two groups (42). Another group used a rabbit model to show that in sterile sinusitis, an increase in airway responsiveness appeared (based on the positioning of the animals) to be related to the postnasal drainage of inflammatory cells or mediators into the lower airway (43). Therefore, the idea of postnasal drainage triggering asthma is worth consideration, but considerably more evidence is needed to support this hypothesis.

Abnormal breathing has also been advanced as a possible causal link between rhinosinusitis and asthma. Because the nose warms and humidifies air and traps particles, oral breathing may lead to inhalation of dry, cold air and environmental pollutants. Griffin et al. (44) demonstrated evidence for such a relationship in patients with asthma. In this study, nine patients with asthma and five healthy controls inhaled subfreezing air through either the mouth or the nose (44). In the patients with asthma, there was better warming of air with nasal respiration and a linear relationship between the degree of air cooling and the drop in FEV₁ (44). Although oral inhalation of cold air impaired lung function in this study, this was probably not the cause of these patients' asthma, because the normal controls that had similar inspiration of cold air showed no decrease in lung function (44).

Another causal relationship between rhinosinusitis and asthma has been suggested by recent research, which points to the possibility that local upper respiratory inflammation may lead to pulmonary inflammation through various mechanisms. Mechanisms for this relationship include increases in cell adhesion receptors and release of chemotactic factors, leading to release of leukocytes from storage pools in the bone marrow and differentiation of the progenitors of these inflammatory cells into mature inflammatory cells, both in the bone

marrow and locally in inflamed tissues (45). For example, in a Dutch study, nasal allergen provocation in a group of nonasthmatic patients with allergic rhinitis resulted in an influx of eosinophils into the nasal epithelium, nasal and bronchial lamina propria, and bronchial epithelium (46). This influx of eosinophils was at least partly mediated by local adhesion molecules because the number of mucosal eosinophils correlated with the local expression of intercellular adhesion molecule (ICAM)-1, E-selectin, and vascular cell adhesion molecule-1 in both nasal and bronchial tissue (46).

Systemic chemokines are also released after nasal allergen challenge. For example, in a murine model of allergic rhinitis, specific nasal challenge with allergen promoted not only a local inflammatory response in the nasal mucosa but increases in eosinophils, basophils, and CD34⁺ cells (hemopoietic stem cells) in the bone marrow (47,48). This response was mediated at least partly by the cytokine IL-5 because nasal eosinophilia was blocked and IL-5-responsive leukocytes in the bone marrow were reduced in IL-5-deficient mice (48).

In a study involving human nonasthmatic patients with allergic rhinitis, inhaled allergen challenge resulted in an increase in sputum eosinophil cationic protein and a rise in IL-5 in the plasma (49). In addition to IL-5, granulocyte macrophage-colony-stimulating factor (GM-CSF) and eotaxin are also implicated as important mediators of communication between the airways and the bone marrow and systemic circulation (50). These mediators are not likely to act as hormones, but they exert local effects that promote the differentiation and maturation of eosinophils, basophils, and mast cells (51).

In addition to IL-5, GM-CSF, and eotaxin, other cytokines, such as IL-4 and IL-13, recruit inflammatory cells into nasal and sinus tissue (52). Then, Th2 lymphocytes from the nasal and sinus tissue likely migrate to the bone marrow, where they stimulate the production and maturation of inflammatory cells (52). For example, studies have demonstrated that

the numbers of IL-5-producing T-cells in the bone marrow increase after inhalation challenge with allergen (53). The activated inflammatory cells that are produced in the bone marrow may then migrate into the pulmonary tissue (52). Activated inflammatory cells may also migrate from inflamed sinus tissue into the circulation and, then, directly into pulmonary tissue (52).

Although there are numerous possible mechanisms by which rhinosinusitis may trigger lower airway responses (e.g., nasopharyngo-bronchial reflexes, postnasal drainage of inflammatory cells and mediators, abnormal air warming and filtration, and increases in cell adhesion receptors and release of inflammatory cytokines after upper airway allergen challenge), a great deal of evidence also supports the concept that rhinosinusitis and asthma are simply local manifestations of systemic inflammatory disease. It appears likely that the true nature of the relationship between rhinosinusitis and asthma is not either simply a triggering phenomenon or simply a systemic disease but is a complex interplay between dynamic local and systemic pathology.

Chronic Rhinosinusitis and Asthma As Manifestations of a Single Disease

In recent years, there has been growing interest in the "one-airway hypothesis," which states that the relationship between upper and lower airway disease is not necessarily causal but instead reflects common histopathology between the two areas. Ponikau et al. (4) recently studied 22 patients with refractory CRS to determine whether typical histopathological features of asthma, such as eosinophilic inflammation, epithelial damage, and basement membrane thickening, are present. This study demonstrated that sinus specimens from all 22 subjects showed heterogenous eosinophilic inflammation, epithelial shedding, and thickening of the basement membrane (4). The damage and inflammation were similar in both allergic and

nonallergic subjects (4). It is likely that eosinophils were important effectors of the damage, because it has been demonstrated that there is an association between the presence of the extracellular deposition of major basic protein (which is produced by eosinophils) and damage to sinus mucosa (54). These features, which are similar to asthma, suggest that a common process underlies at least some types of CRS and asthma (13). This relationship was supported in a study by Harlin et al. (3), in which the investigators examined tissue from patients who underwent surgery for CRS. This study showed that although sinus tissue from patients with sinusitis and concomitant asthma, allergic rhinitis, or both had a large number of eosinophils infiltrated in the sinus tissue, sinus tissue from patients with a history of CRS alone did not (3).

The report that 84% of severe asthmatics have evidence of abnormality on sinus CT provides further evidence for the common change in the sinuses and the lungs (10). In this study, there was a significant correlation between CT scores, eosinophils in peripheral blood, and induced sputum and the level of exhaled nitric oxide, which is a marker of lower airway inflammation (10). An earlier study demonstrated a similar relationship (55). In this study, 104 asthmatic patients who underwent sinus surgery had assessment of sinus CT scans, total serum IgE, specific IgE to common inhalant antigens, and peripheral blood eosinophil count (55). This group showed extensive sinus disease in 39% of the patients and demonstrated that the level of disease correlated well with severity of asthma, presence of specific IgE antibodies, and presence of eosinophilia (55). The researchers also found that 87% of patients with extensive sinus disease by CT had peripheral eosinophilia (55). There is clearly evidence that rhinosinusitis and asthma may be different manifestations of a common disease. Many investigations are currently underway to elucidate the possible mechanisms for this "one-airway" disease (Table 2).

Table 2
Proposed Common Mechanisms for Rhinosinusitis
and Asthma

-
- Bone marrow-mediated airway-wide disease
 - Common response to staphylococcal enterotoxins
 - Common dysregulation of epithelial surfaces
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The bone marrow may provide the link that connects upper and lower airway inflammatory disease into "one-airway" (45). Similarly to the earlier mentioned pathway of local allergen challenge and inflammation in the upper airway stimulating the bone marrow to produce inflammatory cells that have effects on other tissues (such as the lower airways), allergen-induced inflammation in the lower airways can induce upper airway responses (50). One study by Braunstahl et al. (56) examined nonasthmatic allergic patients with rhinitis. After segmental bronchial allergen challenge, there was an increase in eosinophils, basophils, and IL-5 in nasal tissue as well as increased numbers of eosinophils in the blood (56,57). However, rather than acting as a conduit of crosstalk between different parts of the airway, the bone marrow appears to take an active role as a source of inflammatory cells that can infiltrate various areas of the body that are affected by allergic disease (50). A report of transfer of allergic disease into nonallergic individuals following bone marrow transplant supports this view (58). In the bone marrow, the creation of both progenitor and mature eosinophils and basophils that autostimulate by producing their own growth factors, such as IL-5 and GM-CSF, is one of the mechanisms by which bone marrow may maintain an active role in creating systemic allergic disease (50).

Another mechanism that may link CRS and asthma is a common response to bacterial infection. For example, in nasal polyp tissue, Bachert et al. (59) demonstrated IgE specific to staphylococcal enterotoxins A and B. This group also showed that the levels of IgE spe-

cific to enterotoxins correlated with local eosinophilic infiltration (59). In this study, 50% of bilateral nasal polyp tissue demonstrated multiclonal IgE, including IgE specific to staphylococcal enterotoxin A and B (59). Conley et al. (60) recently reported similar results and demonstrated staphylococcal enterotoxin-specific IgE in the serum of 5 of 10 patients with CRS and nasal polyps but none in the serum of the 13 control subjects.

The staphylococcal enterotoxins may act both as local superantigens, which activate a large number of T-lymphocytes, and traditional allergens, which lead to elevated specific IgE levels in the serum (60). Although there is increasing evidence for the role of bacterial enterotoxins in the formation of nasal polyps, the evidence for the relationship between these enterotoxins and inflammatory disease is most clear in the case of atopic dermatitis (61). Bachert et al. (62) also reported preliminary evidence for a role for staphylococcal enterotoxins in the promotion of asthma. In this report, serum IgE levels specific to a staphylococcus enterotoxin mix were found more often in patients with asthma than in controls, and within the group of patients with asthma, they were found more often in patients with severe asthma than in those with mild asthma (62). However, it must be noted that the majority of the patients with asthma also showed symptoms of rhinitis, so this preliminary report may reflect the earlier mentioned findings in patients with CRS and polyps as much as they reflect new findings about patients with asthma (62).

Another example of a possible common mechanism leading both to CRS and asthma is dysregulation of epithelial surfaces of the sinuses and lungs. Holtzman et al. (63) demonstrated this in pulmonary tissue of patients with asthma, in which the adhesion molecule ICAM-1 and the chemokine RANTES were shown to be expressed on epithelial surfaces independent of exogenous stimuli. This dysregulated expression of ICAM-1 and RANTES

facilitates the migration of T-lymphocytes through the epithelium (63). Similar findings have not been reported in CRS, but the similarities between the inflammatory features of CRS with nasal polyps and asthma suggests that a similar mechanism may also play a role in this condition (64).

Redefining Chronic Rhinosinusitis

One of the weaknesses of research on CRS has been the lack of uniform definitions of this disease. This has led to the use of various techniques (e.g., flexible rhinoscopy, sinus X-ray, sinus CT) to establish the presence or absence of CRS and to follow response to treatments, which also have not been uniform (e.g., antibiotics, nasal corticosteroids, systemic corticosteroids, nasal saline irrigation, and various surgical techniques). Additionally, many investigators have limited themselves to radiographic and symptomatic measures to follow response to treatment, whereas others have examined cellular infiltrates and biochemical features of rhinosinusitis, such as adhesion molecule expression and levels of cytokines. The heterogeneity of definitions and techniques in investigations of CRS has led to the tendency to lump all CRS together as a single disorder. However, the evidence is clear that rhinosinusitis may arise from numerous different mechanisms (as described earlier) and, therefore, is the end result of a number of different disorders.

Representing the consensus of a group of 30 experts, Meltzer et al. (64) suggested subdividing CRS into CRS without polyps, CRS with polyps, and classic allergic fungal rhinosinusitis. A further level of subclassification involves the presence or absence of eosinophilic inflammatory features (64). These eosinophilic inflammatory features are present in only a subset of patients without polyps but are almost always present in patients with polyps (64). The pathological processes responsible for CRS with neither polyps nor eosinophilic inflammatory

features include impaired immunity and reduced mucus clearance from the sinuses (64).

In a recent review, Steinke and Borish (52) created their own definition scheme for CRS. The same cases of rhinosinusitis with neither polyps nor eosinophilic inflammatory features described by Meltzer et al. were redefined by Steinke and Borish as infection-driven rhinosinusitis with further subclassification into infectious rhinosinusitis and chronic inflammatory rhinosinusitis (52). Chronic inflammatory rhinosinusitis represents the smallest subset of patients with CRS and typically involves patients with impaired capacity to resist bacterial infection, such as in humoral immunodeficiency and cystic fibrosis (52). Conversely, infectious rhinosinusitis is related to obstructed drainage from the sinuses, leading to recurrent bacterial infection (52). This recurrent bacterial infection leads to damage of the sinus epithelium and inflammatory infiltrate of mononuclear cells but not eosinophils (52). Together, infectious rhinosinusitis and chronic inflammatory rhinosinusitis, as defined by Steinke and Borish, appear to represent truly infectious processes. It is likely that the relationship between these disorders and asthma is related to such causal mechanisms as naso-pharyngo-bronchial reflexes and postnasal drainage leading to bronchoconstriction, rather than different manifestations of a common process.

Unlike the infection-driven types of CRS, CRS with polyps and classic allergic fungal rhinosinusitis are better characterized as inflammation-driven processes (64). CRS with polyps usually has eosinophilic inflammatory features and, therefore, has also been defined as chronic hyperplastic eosinophilic rhinosinusitis (52,64). Approximately 50% of patients with CRS with polyps are allergic, 50% have asthma, and 40% have aspirin sensitivity (64). Allergic fungal rhinosinusitis may represent a severe variant of CRS with polyps in which there is colonization of fungi within the sinuses (52). These conditions may represent a Th2-like process,

with prominent roles for eosinophils and IL-5. Therefore, the link between CRS with polyps or allergic fungal rhinosinusitis and asthma may be both causal (naso-pharyngo-bronchial reflexes and local inflammation leading to stimulation of bone marrow) and different manifestations of a common disease.

For example, it may be useful to understand CRS with polyps as "asthma of the upper airways" (65). Additionally, Venarske and deShazo (66) recently defined a syndrome called "sinobronchial allergic mycosis," in which co-existent allergic fungal rhinosinusitis and allergic bronchopulmonary mycosis represent a common process of fungal hypersensitivity in both the sinuses and the lungs.

Conclusion

The relationship between rhinosinusitis and asthma is complex. There is considerable evidence that rhinosinusitis may act as a trigger for asthma, and numerous plausible mechanisms have been proposed, including naso-pharyngo-bronchial reflexes, postnasal drip, abnormal breathing, and the local production of inflammatory mediators that trigger pulmonary inflammation via the bone marrow. On the other hand, evidence also exists that rhinosinusitis and asthma are manifestations of a common process, with such possible mechanisms as bone-marrow-mediated airway-wide inflammation, common response to staphylococcal enterotoxins, and common dysregulation of epithelial surfaces. This apparent controversy regarding the complex relationship between rhinosinusitis and asthma can be at least partially reconciled by redefining rhinosinusitis with regard to the presence or absence of polyps and the presence or absence of eosinophilic inflammation.

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