Remodeling in Allergic Rhinitis
Adding New Data to an Old Debate

It is well established that patients with asthma develop histologic evidence of airway remodeling, which is characterized by subepithelial fibrosis, increased airway smooth muscle mass, mucous gland and goblet cell hyperplasia, and increased vascularity (1). These histologic changes have been linked to important long-term consequences in asthma, including chronic, minimally reversible airflow limitation and increases in nonspecific airway hyperresponsiveness, both of which may influence the frequency of asthma exacerbations (1, 2). It has been postulated that remodeling is largely the consequence of airway inflammation, also a characteristic of asthma.

Rhinitis is present in the vast majority of patients with asthma, and this comorbidity appears to be stronger when the immunologic background involves allergy (3). In addition, allergic rhinitis bears strong pathogenic similarities to asthma—both conditions are associated with a type 2 pattern of inflammation, with the presence of IL-4, IL-5, and IL-13; mucosal eosinophilia; and evidence of mast cell and basophil involvement (4). The coexistence of rhinitis and asthma and analogous patterns of inflammation has prompted the suggestion that the two conditions are manifestations of a similar disease in different parts of the respiratory tract. Yet the structures of the mucosa and submucosa of the nasal and the lower airways differ significantly (5). For example, the lower airways lack the venous sinusoids that are a characteristic anatomic element of the nasal mucosa, and conversely, the smooth muscle that characterizes the lower airways is absent in the nose. Most importantly, the symptoms of rhinitis are produced by substantially different mechanisms compared with asthma. In allergic rhinitis, exaggerated physiologic responses of the sensorineural apparatus, erectile vasculature, and mucous glands are responsible for the characteristic symptoms of sneezing, pruritus, rhinorrhea, and nasal congestion. This is in contrast to asthma, in which smooth muscle constriction is the dominant mechanism leading to symptomatic lower airway obstruction.

Because of the clinical parallels to asthma and the possibility that allergic nasal inflammation may lead to persistent structural changes in the nose, investigators have searched for evidence of tissue remodeling in patients with allergic rhinitis. During the last 15 years, several publications have examined a number of different indicators of remodeling in nasal tissue, including quantitative assessments of the thickness of the lamina reticularis, the size and density of submucosal glands and goblet cells, collagen protein levels, markers of fibroblast activation, the levels of matrix metalloproteinases, and evidence of vascular proliferation. The results have been conflicting (6).

In the work described in this issue of the *Journal* by Eifan and colleagues (pp. 1431–1439), careful examination of the nasal mucosa using state-of-the-art immunohistology and measurement of mediators of remodeling (e.g., matrix metalloproteinase-9) failed to detect any evidence of remodeling in patients with persistent allergic rhinitis, whether in or out of the pollen season or whether with seasonal or perennial disease, in comparison to healthy control subjects (7). This work adds strong evidence to the concept that mucosal remodeling, at least as it pertains to the targeted structures and molecules, is not present in allergic rhinitis.

Why, then, have other studies suggested that remodeling is present in allergic rhinitis? Methodological issues may be partly responsible, particularly given the subjective aspects of histologic assessment in past investigations as well as differences in assays that have been employed across studies. Another possibility is that environmental exposures, including types and levels of indoor and outdoor air pollutants, may affect both histology and biomarker profiles in individuals with allergic rhinitis, as well as healthy control subjects (8). These factors can vary widely with respect to both geography and season of the year and may have had effects on study endpoints that were not possible to account for. Moreover, it is plausible that these factors have a stronger influence on the nose than on the lower airways, as the nasal mucosa provides the first point of contact with the external environment and serves as a protective filter for the lower airways (4). In a similar fashion, the role of asymptomatic viral infections may also have had important effects on a number of endpoints in studies of nasal remodeling (9). Finally, there may be genetically regulated differences in remodeling processes, related to race as well as other factors, as has been suggested in other airway diseases (10).

Tissue remodeling, as defined earlier, does not appear to be a robust or consistent finding in unselected patients with allergic rhinitis. In response to this, we raise two questions: First, are there other, potentially more important, structural alterations that may play a role in nasal disease, and second, is there a subgroup of patients in whom structural alterations might be more prevalent and pronounced compared with the broader population with rhinitis? In answer to the first question, investigators have noted a significant increase in the density of nerve fibers in the epithelium and subepithelium and around the glands and vasculature of the nasal mucosa in patients with allergic rhinitis compared with healthy individuals (11). This alteration in innervation may have an important, long-term effect on nasal functioning and symptoms in patients with chronic rhinitis. With regard to the second question, there is a small subgroup of patients with rhinitis who suffer from persistent nasal turbinate hypertrophy, which is refractory to medical therapy. A small histologic study of patients with persistent turbinate enlargement showed evidence of subepithelial fibrosis, although this finding was not precisely quantified (12). Ciprandi and colleagues later sought to relate the amount of fixed nasal airflow obstruction to duration of rhinitis (13). Using a cross-sectional study design, they observed that the improvement in nasal obstruction (after instillation of a topical decongestant) was significantly lower in some patients with longer duration of rhinitis. It is possible, therefore, that irreversible nasal airflow obstruction may be related in some individuals to the chronicity of symptomatic disease

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and that remodeling of the nasal mucosa may be more evident in this subgroup of patients. We do need to continue to explore and understand fundamental processes in severe allergic rhinitis; newer and better therapies will undoubtedly emerge. ■

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Dyspnea: Don't Just Look, Ask!

The American Thoracic Society (ATS) official statement defines dyspnea as "a subjective experience of breathing discomfort" (1). We and others have previously urged that healthcare workers should routinely assess and document dyspnea in the same manner as pain. Outpatients most often report experiencing dyspnea during exertion, which can severely limit their activities, but at least this dyspnea can be quickly escaped by ceasing the activity, and that is what patients do: "breathlessness makes you slow right down, like a car running out of gas and it makes you feel exhausted, one has a desire to take a deep breath but the body can't do it" (2). Patients who experience dyspnea in their hospital bed are in a different situation: they cannot escape, and it is up to us to relieve their suffering. Many clinicians, having never personally experienced such inescapable dyspnea, do not fully understand its effect. Listen to what patients have to say about it: "I often thought about death while I was attacked by dyspnea"; "I wondered what's going on with my breathing I asked myself 'will I die here?'"; "I did not have any preparation for those uncontrolled discomforts, and this made me fearful" (mechanically ventilated intensive care unit patients described in Reference 3). "[I]t is a frightened feeling where you don't think you'll get another breath . . . it is accompanied by fear and panic and feeling tight"; "when the shortness of breath was at its extreme, I thought I was going to die and saw a coffin beside me. . . . I did have thoughts about suicide and I envied the dead" (cancer outpatients described in Reference 2).

Our hospital recently began routine documentation of inpatients' dyspnea on the same schedule as pain assessment, both at admission and on each nursing shift (4, 5). We interviewed nurses about the process, and there was wide agreement that the process was easy, quick, and important. We discovered, however, that on some occasions, nurses were not asking the patients to rate how they felt, but, rather, were inferring the intensity of dyspnea from observed signs. The ATS official statement strongly emphasizes that "dyspnea *per se* can only be perceived by the person experiencing it." This statement derives from the definition of a symptom (sensations experienced or perceived by an individual) and provides the basis for distinguishing a symptom from a "sign" (an observed or elicited physical finding). Little evidence is available to refute or support the assertion that clinicians can accurately judge a patient's current breathing discomfort based on observation of behaviors and signs. A seminal report on dyspnea during mechanical ventilation by Lush and colleagues produced "the serendipitous finding that a discrepancy appeared to exist between the patient's perception of his or her own dyspnea

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