Allergic and nonallergic factors in upper and lower airway disease[1]

Henry N. Claman, M.D.

The specific allergic and nonallergic mechanisms that prevail in diseases of the upper and lower airways, e.g., rhinitis and asthma, are reviewed. These mechanisms and diseases are probably not more prevalent in wind players than in others, but they may significantly impair a musician's capabilities. Specific allergic triggers include pollens, molds, dusts, and danders; and the typical immediate inflammatory response to these is mediated by IgE. There is a growing understanding of late-phase reactions, which are triggered by IgE but which occur four to 12 hours after antigen exposure. Specific allergic responses may occur with or without nonspecific, non-IgE reactions, which include responses to a wide variety of irritants including cold air, particulates, and infections. There is a growing realization that host responses to specific allergens and nonspecific irritant factors can influence and accentuate each other. Treatment should be directed toward identification and avoidance of both kinds of triggers. Immunotherapy is sometimes required.

Index terms: Music · Respiratory hypersensitivity

Cleve Clin Q 53:21–25, Spring 1986

Allergic diseases of the upper and lower airways are common and occur in all age groups, particularly in the young. The discovery of IgE as the immunoglobulin class responsible for classic anaphylaxis, allergic rhinitis, and allergic asthma has permitted much greater understanding of the mechanisms of allergic inflammation, e.g., the release of histamine and other mediators. More recently, investigators have been exploring the interactions of specific antigenic triggers with nonspecific stimuli, e.g., irri-

[1] Division of Clinical Immunology, Department of Medicine, University of Colorado School of Medicine, Denver. Submitted for publication Apr 1985; accepted July 1985. lp

0009-8787/86/01/0021/05/$2.25/0

tants, certain infections, and chemicals. These interrelations are important in allergic disease of both the upper and lower airways.

Upper airways

Allergic rhinitis

This is the purest example of an immediate allergic hypersensitivity reaction of the airways.

Immediate allergic factors: Typical allergic rhinitis is almost always IgE mediated. The pathophysiology is well understood. IgE antibodies develop in response to specific antigens, which are almost always inhalants. Antigens reach the nasal mucosa and react with IgE molecules on the surface of tissue mast cells. These cells release their granules, which contain a variety of mediators, chiefly histamine. Histamine release results in local edema, vasodilatation, fluid secretion, sneezing, rhinorrhea, and partial obstruction. Antigens include seasonal pollens, molds (seasonal and nonseasonal), and perennial antigens, e.g., household animal danders, feathers, and house dust. Foods are rarely important in pure allergic rhinitis.

Late allergic factors: Only recently have investigators noted that the mucosal responses in IgE-mediated diseases may not all be acute. There are late-phase reactions (LPRs) in which inflammatory changes occur four to 12 hours after the initial insult. These reactions have been more extensively studied in the lung than in the nose, as will be discussed in the section on lower airways. Nevertheless, as the lung and the nose react similarly in these situations, there is no doubt that LPRs also occur in the nose. As in the lung, they contain more inflammatory cells than the immediate phase reactions (which are primarily edematous).

Nonspecific (nonallergic) factors: Patients with ragweed-induced allergic rhinitis may complain that cigarette smoke bothers their nose or eyes during August and September but not in the winter. Additional nonspecific irritants include chemical fumes and strong odors, cold air, and viral infections. There is no doubt that the IgE-mediated inflammation (both the immediate and the late phase) sensitizes the nose to nonspecific irritants. The physiological basis for this reinforcement reaction is not known. It is also possible, although even less well understood, that nonspecific irritant reactions in the mucosa of the upper airways may promote sensitization or triggering of IgE-mediated specific allergic reactions or both. Much remains to be learned about the interrelations between specific and nonspecific precipitants of upper airways mucosal diseases.

Vasomotor rhinitis (VMR)

"Vasomotor rhinitis" is an old term for a poorly understood condition (or group of undifferentiated conditions). The primary symptoms are nasal obstruction, often unstable, without much sneezing, itching, or rhinorrhea. The lack of the latter symptoms indicate that histamine is not a likely mediator and IgE mechanisms are not operational. Indeed, eosinophils, which are so common in the nasal secretions in classic allergic rhinitis, are not prominent in VMR secretions, and this fact is often used as an indicator in the differential diagnosis. Patients with VMR complain about the nonspecific irritants mentioned previously. Their nasal obstruction is aggravated by agents such as smoke, odors, cold air, dryness, and viral infections. It is not clear whether or not there is a disturbance of vasomotor control of the mucosa in this condition. Physicians treating these patients believe that emotional triggers may be important, and this concept has firm experimental backing.[1]

Rhinitis medicamentosa

Patients may easily overuse nasal decongestant sprays and drops, which are increasingly available. This condition is frequently overlooked as a possible cause of the stuffy and runny nose. Because simple, reliable, and objective ways to measure nasal airflow or airways resistance are not yet available, physicians must rely on history and physical examination for this condition and for VMR. Some patients are so addicted to nasal decongestants that nasal or oral corticosteroids or both are required for weaning.

Nasal polyposis

Patients with this syndrome include sufferers from several conditions. Many cases are clearly associated with chronic or recurrent infection of the paranasal sinuses, and thus are not considered as allergic diseases. In some patients with uncontrolled IgE-mediated allergic rhinitis, nasal polyps and indications of excessive mucosal edema and hyperplasia may develop. In this situation, their triggers would be the same as those of uncomplicated hay fever, but there would be

greater degrees of obstruction and fewer (if any) periods of freedom from nasal symptoms, even outside that individual's allergy season.

Triad asthma

Finally, there are those fascinating cases of triad asthma. The classical triad includes asthma, nasal polyposis, and idiosyncratic reactions to acetylsalicylic acid (ASA).[2] The reactions to ASA may be devastating attacks of asthma and rhinitis, some of which have been fatal. Although the condition has been recognized for more than 60 years, it is not completely understood. It is clear that antibodies to ASA are not involved. An important discovery was that many of these patients are sensitive not only to ASA, but also to other nonsteroidal anti-inflammatory drugs (NSAIDs), particularly indomethacin.[2] This drug has no structural similarity to ASA, but both drugs inhibit the cyclooxygenase pathway of arachidonate metabolism. Therefore, it is widely believed that patients with triad asthma have some abnormality of prostaglandin metabolism. There appears to be no association between triad asthma and atopic (IgE-mediated) disease. Some patients with triad asthma are clearly atopic, with positive family histories for hay fever, asthma, etc, and significant immediate wheal-and-flare skin tests to common allergens. However, other patients with triad asthma are not atopic. A few atopic patients who are also ASA-sensitive can remember when their ASA sensitivity became superimposed on their atopic allergies. It would be helpful to learn what caused the switch in prostaglandin metabolism and ASA sensitivity.

Lower airways

Allergic laryngitis and tracheitis

Although allergic laryngitis and tracheitis undoubtedly exist, they are not often diagnosed. First, these conditions in their pure state are uncommon. The mucosa of the vocal cords is squamous and may indeed resist IgE-mediated inflammation. Second, diagnosis may be difficult as the vocal cords may look normal but be abnormal. Furthermore, cough, the primary symptom of allergic tracheitis, is also prominent in typical asthma and may be overshadowed by lower airway obstruction. However, it should be recognized that there are territorial limits in allergic airway diseases. Some patients may have only rhinitis from a particular antigen, whereas others may have only asthma from the same antigen, and still others may have both syndromes. It is not known whether the larynx and the trachea can be singled out as anatomic targets for IgE-mediated illness, and, if they can, what determines the location.

Allergic asthma

This common syndrome may be defined as antigen-triggered reversible airways obstruction associated with hyperreactivity of those airways. About 6% of school-age children have asthmatic symptoms, at least half of which are IgE mediated. Fortunately, the symptoms are often mild. The airways hyperreactivity is always present in asthmatics, but may be less apparent when they are asymptomatic. It also may be present in some asymptomatic first-degree relatives. Nevertheless, the genetics of this syndrome, as well as of IgE-mediated disease in general, is not well understood. The tendency to overproduce IgE is not a simple Mendelian trait.

The underlying basis of airway hyperreactivity is also not well understood. It might be an imbalance between vagal influences (mediating bronchoconstriction) and beta-adrenergic influences (mediating bronchodilatation).

Demonstration of airway hyperreactivity: Asthmatic airways respond with bronchoconstriction to a variety of provocative stimuli, but always at doses insufficient to provoke bronchoconstriction in normal airways.[3] These stimuli include pharmacologic agents, such as histamine and methacholine; immunologic agents, such as the relevant antigen in IgE-mediated asthma; chemical agents, such as SO_2, citric acid, and even distilled water; and thermal stimuli, such as cold air. Psychologic stimuli may also be provocative but are less easy to standardize and administer.

Clinical inducers of bronchoconstriction: Outside of the pulmonary laboratory, asthmatics may respond to a wide variety of stimuli with bronchoconstriction as well as edema, mucus production, and inflammation of the lamina propria These agents include air pollutants of all kinds, both gaseous and particulate; exercise (probably via cooling the airway); viral infections; drugs including ASA, NSAIDs, tartrazine (FDA yellow #5, a coloring additive), sodium metabisulfite (an antioxidant added to foods); and specific allergens. Viral respiratory infections are particularly detrimental to asthmatics, probably because they damage the superficial mucosa of the airways and

perturb irritant receptors in the vagal system. By contrast, asthmatics may have pneumococcal lobar pneumonia without any bronchospasm at all.

Early and late specific reactions

The immediate bronchoconstrictive response to inhaled atopic allergen has been known for many years. It is now apparent that these reactions may be followed by LPRs of an inflammatory nature, which occur four to 12 hours after the early reaction.

Immediate airway reactions: Upon aerosol challenge with the appropriate allergen, the asthmatic shows a rapid fall in forced expiratory volume (FEV) and a rise in airway resistance, generally within 30 minutes. This is caused by a typical IgE-mediated mast cell degranulation reaction in the lung, which is the pulmonary counterpart of the immediate wheal-and-flare reaction in the skin. Histamine is released, and there is also the production of leukotrienes including what was formerly called slow-reacting substance of anaphylaxis (SRS-A), prostaglandins, and eosinophil and neutrophil chemotactic factors. Physiologically, there is bronchial smooth muscle constriction, increased mucous secretion, mucosal edema, and eosinophilia. This reaction is typically self-limited and resolves in 60 to 120 minutes. The changes can be prevented by premedication with antihistamines (H-1), beta-agonist bronchodilators, or cromolyn but *not* by corticosteroids.

Late-phase airway reactions: If studied carefully, many patients with allergic asthma show a later fall in FEV, which occurs two to 10 hours after the effects of the immediate inhalation challenge to antigen has resolved. These LPRs are being increasingly recognized in the lungs, the nose, and in the skin.[4] For example, after demonstrating to a class of medical students that I had a large immediate wheal-and-flare skin-test reaction on my arm to juniper pollen extract, I found later that evening that I also had a large (and tender) LPR to juniper that lasted well over 24 hours.

Results of biopsy of the skin in LPRs show subacute inflammation with more cellular infiltrate and less edema than is seen in the immediate phase. It is critical to understand that these responses in general follow and depend upon prior immediate responses. As LPRs can be provoked by injection of mast cell granules,[5] it is likely that they are induced by production and release of mast cell mediators involved in the immediate phase of this dual reaction. Late-phase reactions may be inhibited by pretreatment with corticosteroids; this emphasizes their difference from the immediate reactions.

Interrelation between specific allergic reactions and nonspecific airway hyperreactivity: This important but complex topic is just being explicated. It covers the possibilities that allergen provocation may influence nonspecific airway irritability or vice versa. One striking example of the former possibility was recently demonstrated by Cockcroft.[6] He measured the specific (dual) airways response to ragweed antigen inhalation in a ragweed-sensitive asthmatic, and also measured the nonspecific bronchial hyperreactivity by graded dose-response tests to inhaled methacholine. He found that before ragweed challenge, the patient had a modest bronchospastic reaction to inhaled methacholine. After inhalation of ragweed antigen had induced a dual (immediate and late) bronchial response from which the patient easily recovered, the patient's sensitivity to mecholyl inhalation was tenfold greater. Furthermore, this antigen-induced nonspecific airways hypersensitivity lasted more than seven days after the specific ragweed inhalation challenge.[6] Further study is necessary to explain this remarkable effect.

The role of allergy in asthma

The controversy regarding the role of allergy in asthma is reflected in the differing views of allergy and pulmonary specialists. Allergists are often viewed by pulmonary specialists as finding allergy when it is not present (or is not important) and, conversely, pulmonary specialists are viewed by allergists as not finding allergy because they do not look for it. The truth lies in between.

Asthma is not a disease, but a syndrome. It appears to have a bimodal prevalence pattern, i.e., with peaks at about ages 10 and 60. This suggests at least two patterns of reactivity. IgE-mediated asthma is a reality, and it is more prevalent in younger patients. Intrinsic asthma (older term) or nonallergic chronic obstructive pulmonary disease is more common in patients more than 50 years of age. These patients, if they ever had IgE-mediated disease, either often have it no longer or have it overshadowed by bronchitis, emphysema, and the effects of cigarette smoking. Physicians who see younger patients consider IgE more than those who see older patients.

If allergy is defined as IgE-mediated illness, it is limited to only some asthmatics; however, if the definition is broadened to include reactions to ASA, exercise, metabisulfite, it then encompasses a wider group of asthmatics.

Treatment

Avoidance of identified triggers is the preferred treatment for the upper and lower airway diseases discussed in this paper. These triggers include specific allergens or nonspecific factors whether they are allergy-inducing or not, and whether or not IgE mechanisms are involved.

Symptomatic treatment is needed when avoidance is not sufficient. β-adrenergic bronchodilators often cause tremors, and antihistamines may produce an uncomfortable dry mouth, which may make these medications of limited use in musicians. It is fortunate that there is a wide variety of these preparations available, and a trial of several may be needed before the optimal drug and optimal dosage are found. Corticosteroids are free of both of these side effects, and they can be given orally, nasally, or bronchially. The dangers of prolonged systemic steroid therapy are well appreciated. Now alternate-day oral maintenance doses or local steroid inhalations for the nose or the lungs can be used. Once-monthly injections of depot steroids are effective anti-inflammatory agents, but most physicians believe that the risk of serious hypothalamic-pituitary-adrenal suppression is too great. These agents may be used occasionally but should not be given on a regular schedule. Cromolyn sodium is available for inhalation for asthma and in nasal and ophthalmic preparations for hay fever.

Immunotherapy for asthma is still controversial 73 years after it was first introduced. The ability to desensitize IgE-sensitized subjects has a firm foundation in the experimental immunology laboratory. Immunotherapy has been tried in enough prospective, randomly assigned, double-blind studies of allergic rhinitis to establish its efficacy in that condition.[7] However, there are conflicting reports regarding the efficacy of immunotherapy in allergic asthma. Whereas at least one study shows it is not effective,[8] another less-flawed investigation shows that it is.[9] The present method of immunotherapy is neither simple nor inexpensive, but work is in progress to develop better methods, using other types of antigenic extracts.[10]

β-blockers, musicians, and potentiated anaphylaxis

Musicians (and other performers) often use β-adrenergic blocking drugs before auditions or performances to diminish anxiety-associated tremors. It is well known that such medications can increase bronchospasm in asthmatic patients. Even more serious problems have recently been recognized, however. Anaphylactic reactions can be prolonged, severe, and difficult to treat if the patient has been taking β-blockers. This situation has been observed in reactions to insect sting and to allergy immunotherapy. This syndrome has been called "potentiated anaphylaxis."[11,12]

Professor of Medicine and of Immunology
and Microbiology
Head, Division of Clinical Immunology
University of Colorado School of Medicine
4200 East Ninth Avenue
Denver, CO 80262

References

1. Holmes TH, Goodell G, Wolf S, Wolff HG. The Nose: An Experimental Study of Reactions Within the Nose in Human Subjects During Varying Life Experiences. Springfield, Ill, Charles C Thomas, 1950.
2. Settipane GA. Aspirin and allergic diseases: a review. Am J Med 1983; **74**(suppl 6A):102–109.
3. Boushey HA, Holtzman MJ, Sheller JR, Nadel JA. Bronchial hyperreactivity. Am Rev Respir Dis 1980; **121**:389–413.
4. Dolovich J, Hargreave FE, Chalmers R, Shier KJ, Gauldie J, Bienenstock J. Late cutaneous allergic responses in isolated IgE-dependent reactions. J Allergy Clin Immunol 1973; **52**:38–46.
5. Oertel HL, Kaliner M. The biologic activity of mast cell granules. III. Purification of inflammatory factors of anaphylaxis (1F-A) responsible for causing late-phase reactions. J Immunol 1981; **127**:1398–1402.
6. Cockcroft DW. Mechanism of perennial allergic asthma. Lancet 1983; **2**:253–256.
7. Norman PS. Immunotherapy. [In] Ishizaka K, ed. Progress in Allergy. Basel, S Karger, 1982, vol 32, pp 318–346.
8. Bruce CA, Norman PS, Rosenthal RR, Lichtenstein LM. The role of ragweed pollen in autumnal asthma. J Allergy Clin Immunol 1977; **59**:449–459.
9. Taylor WW, Ohman JL, Lowell FC. Immunotherapy in cat-induced asthma: double-blind trial with evaluation of bronchial responses to cat allergen and histamine. J Allergy Clin Immunol 1978; **61**:283–287.
10. Hendrix S, Zeiss CR, Levitz D, Suszko IM, Patterson R. Polymerized whole ragweed: a two-year follow-up of patients treated with an improved method of immunotherapy. J Allergy Clin Immunol 1980; **65**:57–60.
11. Jacobs RL, Rake GW Jr, Fournier DC, Chilton RJ, Culver WG, Beckmann CH. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. J Allergy Clin Immunol 1981; **68**:125–127.
12. Hannaway PJ, Hopper GDK. Severe anaphylaxis and drug-induced beta-blockade (letter). N Engl J Med 1983; **308**:1536.