

How the current understanding of the pathophysiology of asthma influences our approach to therapy

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Asthma can no longer be equated with bronchospasm; instead, we know now that this disease is due to combinations of mucosal edema and inflammation, increased secretions, and muscle contraction. The appreciation of the contribution of these various causes of airflow obstruction and the role that inflammation plays in asthma dictates that we approach treatment using two parallel modalities: (1) symptomatic drugs that act to relieve the airflow obstruction but have no effects on the underlying causes of the disease (e.g., bronchodilators such as β -adrenergic agonists, theophylline, and anticholinergic compounds) and (2) specific treatment aimed at preventing or reversing the underlying causes responsible for the disease. Four specific treatments are available today: allergen avoidance, immunotherapy, cromolyn sodium, and inhaled corticosteroids. Management of asthma in the 1990s requires that all patients receive specific treatments intended to reduce the disease processes and that symptomatic treatment be used only as necessary. (J ALLERGY CLIN IMMUNOL 1993;92:144-7.)

One working definition of asthma is a disease of reversible inflow obstruction manifested as wheezing and caused by various combinations of airway mucosal edema and inflammation, increased secretions, and smooth muscle contraction. Asthma patients exhibit airway hyperreactivity, and the clinical course is variable.

The primary pathologic changes causing airflow obstruction in asthma have been documented for some time.² However, our new appreciation of the importance of airway inflammation and its effects on airway hyperresponsiveness have radically altered our approach to the treatment of asthma. The lungs of asthma patients who have died in status asthmaticus show the following changes: epithelial denudation, goblet cell hyperplasia, basement membrane thickening, eosinophil and neutrophil infiltration of the lamina propria, muscle hyperplasia with evidence of contraction, and glandular hyperplasia with evidence of hypersecretion. The airway lumen contains excessive secretions, eosinophils, neutrophils, Creola bodies, Curschmann's spirals, and Charcot-Leyden crystals. Recent studies describing biopsy specimens

obtained from asthma patients have confirmed that edema and denudation of the mucosa, eosinophil and neutrophil infiltration, basement membrane thickening, and mast cell hyperplasia and degranulation are found even in patients with mild ambulatory asthma.^{3, 4} Thus the airways of asthma patients exhibit a striking degree of inflammation and other changes even when the patient feels well.

There is a current controversy regarding the genesis of this inflammation. One group suggests that mast cell-initiated late-phase reactions are the cause of this inflammation. The late-phase reaction was appreciated after antigen inhalation challenge and was initially thought to be due to an Arthus-type reaction. However, careful studies in human beings and in animals⁵ revealed that the reaction was due to mast cell mediators. Indeed, mast cell mediators could reproduce the inflammatory response. It is now believed that mediators including inflammatory factors of anaphylaxis, neutrophil chemotactic factors, and platelet activating factor cause the infiltration of neutrophils and eosinophils at the site of mast cell degranulation. Recent evidence that mast cells induce the expression of adhesion molecules on the surface of endothelial cells⁶ and that this expression is increased in asthma⁷ supports this concept.

Another group agrees that late-phase reactions are initiated by allergen inhalation challenge but argues that it is the macrophage activated through

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its low-affinity IgE receptor that reacts, releasing products that are responsible for the late-phase reaction.⁸ The data supporting this concept are based largely on data from animal experiments or experiments employing human peripheral blood monocytes, and there is scant evidence that human alveolar macrophages may be activated by antigen *in vivo*.⁹ Lymphocytes are also potentially involved in the late-phase reaction, as well as participating in regulation of mast cell number and IgE production.

Recent studies showing that mast cells synthesize and release several important cytokines capable of causing or facilitating an inflammatory response have contributed to the controversy. These cytokines include interleukin 3, interleukin 4, interleukin 5, tumor necrosis factor, interferon- γ , and others.^{10, 11} These mediators appear several hours after antigen exposure and may contribute to late-phase responses. Moreover, basophil infiltration with subsequent release of mediators may also contribute to the late response. Current work suggests that basophils infiltrate the skin and nasal mucosa during the late response, and there is at least some indication that basophils are found in bronchoalveolar lavage fluid from asthma patients undergoing late-phase reactions. In human nasal and cutaneous models there is substantial evidence that mast cells (or perhaps basophils) are reactivated during the late response and that this response is one of the targets for allergy immunotherapy.⁵

The presence of airway inflammation has influenced our understanding of the dynamics of the disease. One major insight is the relationship between allergen-induced late-phase reactions and increased airway reactivity. It has been observed and confirmed that allergen challenge in the laboratory and natural seasonal allergen exposure lead to increased airway reactivity. Conversely, reduction in allergen exposure reduces airway reactivity.⁵ Airway hyperreactivity appears to play a major role in asthma, predating and predicting the disease, and is closely correlated with both symptom scores and medication requirements. It is therefore appropriate to include airway reactivity as one of the targets for the treatment of asthma. On the basis of this concept, therapy should be aimed at the underlying causes of the disease rather than at simply reducing airflow obstruction.

It has been shown that avoidance of allergens in dust-allergic children with asthma results in improvements both in airflow obstruction and in

airway reactivity.^{12, 13} These findings confirm the relationship between allergen exposure and increasing airway reactivity. The implication is that reduction in allergic reactions should benefit allergen-sensitive asthma patients. There is little controversy regarding the role of immunotherapy in the treatment of allergic rhinitis caused by pollens and dust. However, considerable controversy surrounds the use of immunotherapy in asthma. Many studies have been published on this topic, and the literature contains both positive and negative reports. The factors responsible for the various outcomes relate to asthma itself, a disease that is far more complex than rhinitis. The recent literature suggests that if one chooses relatively "pure" allergic asthmatic patients, such as cat allergen-sensitive subjects, then the data are relatively straightforward. Immunotherapy with purified cat allergen improves asthma in cat-allergic asthma patients.^{14, 15} Other studies using airway reactivity as the endpoint for immunotherapy have also shown improvement.¹⁶ Thus immunotherapy may be used appropriately in allergic asthmatic patients to treat their underlying allergies, and with time this treatment will reduce both asthma and the associated increased airway reactivity. Moreover, immunotherapy is the only modality available today that has a long-lasting response, reducing the needs for all other medications when effective.

Cromolyn sodium is an agent whose precise mode of action remain unclear but that has the ability to reduce mast cell reactivity. Given prophylactically, cromolyn sodium can prevent allergen-induced early asthmatic responses, late asthmatic responses, and the increased airway reactivity that ordinarily results from these challenges.¹⁷ Although there is some controversy about the capacity of cromolyn sodium to reduce airway hyperresponsiveness, in general, studies conducted for longer than 4 weeks show improvement in airway reactivity.¹⁸ A study by Petty et al.¹⁸ performed in adult patients with chronic asthma demonstrated impressive gains in both airway reactivity and symptom scores. Nedocromil sodium, a pyranoquinoline, is another nonsteroid antiinflammatory agent for the treatment of asthma. Clinical studies in allergic and nonallergic adult asthmatic patients have shown that nedocromil sodium improves asthma symptoms and decreases bronchial reactivity.¹⁹

Corticosteroids have many actions that make them useful in treating asthma. Among the most relevant actions are reduced microvascular per-

1970–1990 → ERA OF SYMPTOMATIC TREATMENT

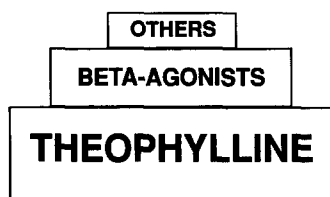


FIG. 1. Era of symptomatic treatment of asthma: From 1970 to 1990 asthma therapy was based on symptomatic control using theophylline as first-line medication. If patients required additional medications, β -agonists were used. Cromolyn eventually became more popular but was usually an "additional" agent rather than primary treatment. Inhaled corticosteroids became available late in the era and heralded the start of the next major change in asthma treatment.

meability, reduced mucus secretion, reduced prostaglandin production, enhanced β -adrenergic responses, reduced mast cell number and reactivity *in vivo*,²⁰ reduced late-phase responses, and reduction in airway reactivity.²¹ Thus topical corticosteroids have become more and more useful in asthma therapy.

A NEW ERA IN ASTHMA THERAPY

One can divide asthma therapy into two eras. The first, the era of symptomatic control, runs from 1970 to 1990. During this period β -adrenergic agents specific for the β_2 -receptor were developed, modified, and made available for convenient and effective bronchodilation. Theophylline was formulated into extremely convenient timed-release preparations, which, when combined with accurate and convenient measurements of serum theophylline levels, led to the great popularity of this compound in the United States. Indeed, theophylline products became the foundation for the treatment of asthma²² (Fig. 1). It was commonly taught in the United States that chronic asthma was best controlled by employing theophylline as the foundation for clinical control, to which β -agonists were added if additional bronchodilation was necessary. Late in this period, ipratropium bromide became available both for bronchodilation and to inhibit mucus secretion. This approach to asthma management was successful for the treatment of most patients, although both hospitalization and death rates increased.

Just before 1990, a new era in asthma therapy began in the United States (Fig. 2). This era is based on the use of specific therapy as the foundation for asthma treatment and includes the

1990 → ERA OF SPECIFIC TREATMENT

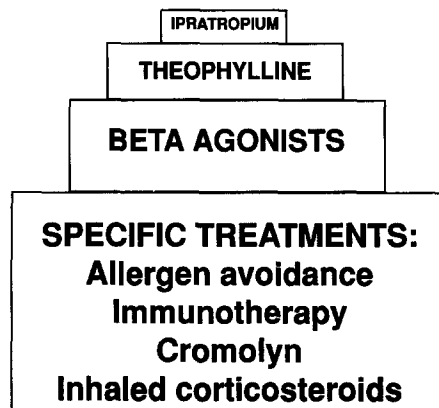


FIG. 2. Era of specific treatment: From 1990 asthma therapy entered a new phase in which the primary approach to treatment uses agents intended to treat underlying causes of asthma, not just symptoms. This era is just beginning but is based on early use of allergen avoidance, allergy immunotherapy, inhaled corticosteroids, and cromolyn (or nedocromil) as first-line treatment. Bronchodilators are used as needed to control symptoms, with β -agonists by inhalation being used first and theophylline next. Ipratropium is indicated as both a bronchodilator and as an inhibitor of mucous secretion.

conceptual corollary that the use of symptomatic agents be restricted to an "as needed" basis. Thus patients start receiving one or more specific treatments, depending on the individual pattern of disease, and are also given symptomatic agents as needed. The specific treatments are intended to reduce the underlying cause of the disease and, if successful, should reduce the need for concomitant symptomatic medication.

What are the expectations for this new approach? The long-term use of cromolyn sodium, inhaled corticosteroids, and allergen avoidance (and probably immunotherapy as well) reduce both airway hyperreactivity and asthma symptoms. In most patients this treatment results in a decreased need for bronchodilators. If such treatment is completely successful, patients will eventually require few or no medications to control their disease. This expectation is for the bulk of the population with asthma and not necessarily for the patient with severe asthma who often requires oral corticosteroids on a daily basis. However, even in the extreme patient, our experience is that careful attention to not only the airways, but also to the sinuses and any potential acid regurgitation into the esophagus reduces the need for oral corticosteroids.

Both logic and experience dictate that the new

approach to asthma therapy will help many patients reduce their need for bronchodilators. However, one possible unwanted effect of this new approach is that the use of theophylline may become more restricted than is appropriate. Theophylline is an extremely effective bronchodilator. Although there are some side effects and concerns about its use,²³ these concerns do not proscribe its use but instead suggest appropriate precautions in use. To put the current shifting of opinion into proper context, it is not appropriate to "throw the baby out with the bath water." Thus theophylline is an extremely useful symptomatic agent to treat chronic asthma and should be added to specific treatment and β -agonists when the patient's asthma is not properly controlled or when a long-acting, reliable bronchodilator is needed.

We are entering a period when various anti-inflammatory agents are being studied in the treatment of severe asthma. Medications such as cyclosporin appear to have some possible use as well. Pharmaceutical companies are examining the usefulness of leukotriene antagonists, platelet activating factor receptor blockers, 5-lipoxygenase inhibitors, mucolytics, and the like in asthma therapy. It is certain to be a time of change. However, the greatest advance has been the change in the aim of therapy. Until recently we simply tried to control the symptoms of asthma. Now, it is conceivable that for the majority of asthma patients we should be aiming at reducing the disease itself, not just providing symptomatic control. This basic conceptual change will have profound effects on asthma therapy and perhaps on the morbidity and mortality of the disease as well.

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