

## Managing Asthma in Adults

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### **Abstract**

***Asthma is a chronic inflammatory disorder of the airways with a spectrum of presentations—from intermittent but mild symptoms to persistent symptoms with chronicity. The key to successful management of the disease process is not only to treat the acute symptoms of wheezing, breathlessness, chest tightness, and cough but also to suppress the underlying inflammatory component. Management requires an integrated approach that incorporates patient education, control of environmental triggers, the judicious use of an appropriate agent to suppress underlying inflammation, addition of adjunctive therapy to optimize primary control, and the supplemental use of a bronchodilator to control breakthrough symptoms. Inhaled corticosteroids are the most effective agents for primary control of patients with persistent asthma. The nonsteroidal antiinflammatory agents cromolyn and nedocromil are alternative choices for primary control. Adjunctive or secondary controllers include maintenance bronchodilators such as salmeterol and long-acting theophylline as well as leukotriene modifiers. Concurrent therapy with an inhaled corticosteroid and a long-acting beta agonist has been shown to provide better asthma control than therapy with either an inhaled corticosteroid plus a leukotriene modifier, an inhaled corticosteroid plus theophylline, or higher doses of an inhaled corticosteroid alone.***

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**A**sthma is a heterogeneous disease process in which both hereditary and environmental factors contribute to the development and expression of the clinical symptoms experienced by the patient. A variety of triggering factors can incite exacerbations of symptoms. The disease is an entity with a spectrum of presentations, from intermittent but mild symptoms to persistent symptoms with chronicity.

The National Heart, Lung, and Blood Institute (NHLBI) and World Health Organization Global Initiatives for Asthma Workshop report defines asthma as “a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils, and T lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli.”<sup>1,2</sup>

The key to successful management of the asthmatic disease process is not only to treat the acute symptomology but more importantly to suppress the underlying inflammatory component, which results in a reduction in bronchial hyperresponsiveness; attenuation of diurnal variability, with improvement in lung function; and a

reduction in the chronic symptoms of asthma.

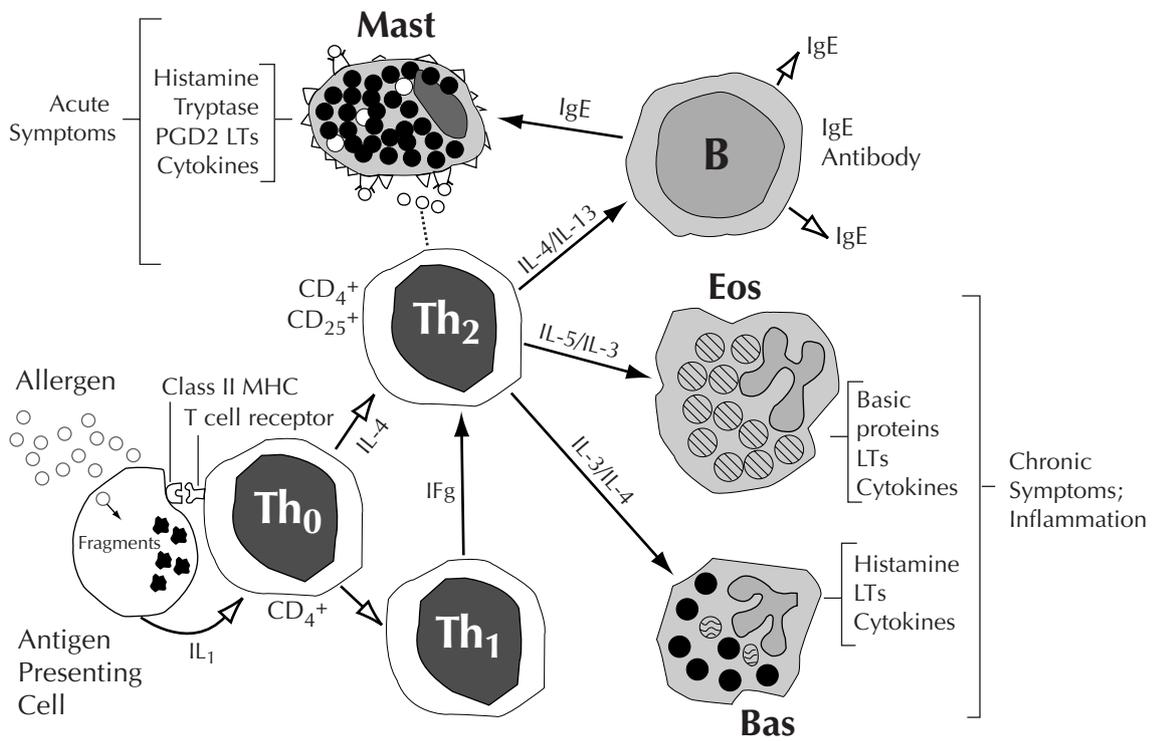
**Pathophysiologic Features**

Allergic asthma serves as a primary model for understanding airway inflammation. The acute (immediate) allergic response results in IgE-dependent mast cell activation, preformed mediator release (eg, histamine), and newly generated synthesis of mediators from the arachidonic acid pathway (eg, leukotrienes and prostaglandins). Coincident with this process, allergen is also taken up and processed by antigen-presenting cells (eg, macrophages and dendritic cells) with the presentation of specific peptide sequences to T lymphocytes. In the allergic patient, costimulatory

signals induce clones of CD4<sup>+</sup> TH<sub>2</sub><sup>+</sup>-type T cells to express specific cytokines (IL-3, IL-4, IL-5) that can have direct effects on a variety of inflammatory cells (mast cells basophils, eosinophils), as well as antibody-producing B cells to further enhance cell-to-cell interactions (Figure 1).<sup>3,5</sup>

These complex cellular events lead, on one hand, to acute clinical symptoms and perhaps of more critical relevance to the underlying allergic inflammatory cascade to a late phase of reactivity, which is the result of cellular recruitment and mediator release, with a recrudescence of clinical symptomatology. Hence, as a result of chronic exposure to a relevant allergen, the IgE-mediated allergic cascade is

**Figure 1.** Schematic of Allergic Inflammation



Source: Creticos PS. Peptide down regulation of the immune response. In: Marone G, Austen FK, Holgate ST, Kay BA, Lichtenstein LM, eds. *Asthma and Allergic Diseases*. Academic Press, Harcourt Brace and Company Publishers;1998:407-415. Reprinted with permission.

a reflection of an immediate phase of reactivity with the subsequent development of a late-phase response that in many patients leads to chronic inflammation. This chronic inflammation is recognized as the subsoil for persistent clinical symptoms and oftentimes the development of non-specific airway hyperresponsiveness, whereby not only the relevant allergen(s) but also nonspecific irritants (pollutants, cigarette smoke, cold air) become factors capable of triggering symptoms.<sup>3-5</sup>

Laboratory methods that use skin, nasal, or bronchial provocation provide the opportunity to characterize this clinical allergic response and to further investigate the underlying cellular and biochemical inflammatory process. Varney et al used skin and nasal biopsy specimens to study severe grass-allergic rhinitis. Biopsy specimens from these patients with allergen-induced late-phase cutaneous responses demonstrated an infiltration of CD4<sup>+</sup> T lymphocytes (granulocyte-macrophage colony-stimulation factor, IL-3), T<sub>H2</sub><sup>+</sup>-type cytokines (IL-4, IL-5), and recruitment and activation of eosinophils.

Various investigators have used nasal provocation with allergen to induce the acute clinical symptoms of allergic rhinitis and have shown that it correlates with the appearance of various inflammatory mediators (eg, histamine, prostaglandins, leukotrienes, and kinins) in nasal secretions. In a significant percentage of these allergic patients, a recrudescence of symptoms occurs approximately 6 to 11 hours after allergen provocation. This late-phase response is characterized by secondary recruitment of certain inflammatory cells (eosinophils, basophils), resulting in a secondary wave of inflammatory mediators. This not only results in a persistence of airway inflammation but also appears to play a role in the development of heightened airway responsiveness not only to specific

allergic stimuli but also various non-specific irritant stimuli.<sup>7-9</sup>

Using bronchial provocation with ragweed, it is possible to demonstrate the same characteristic pattern of an immediate allergen-induced response followed by a late-phase bronchial reaction with a similar profile of inflammatory mediators in bronchial lavage fluids from subjects with allergic asthma. Casale and colleagues<sup>10</sup> used a model of bronchial allergen challenge to provide evidence for a mast cell-derived mediator (ie, histamine) as a basis for antigen-induced bronchial constriction. Liu and colleagues<sup>11</sup> have performed a segmental allergen challenge and demonstrated a significant increase in the number of T cells, basophils, and eosinophils in the lungs at 18 hours post bronchial challenge. This observation correlates with the presence of specific inflammatory mediators from these cells in the bronchoalveolar lavage fluids.

The clinical correlates of the pathophysiologic changes induced by the inflammatory mediators elaborated from these various cells are observed as increased mucus production, mucosal edema, and epithelial damage in the asthmatic's airways. If persistent, this inflammation leads to various alterations in the airways, including a thickening of mucosal and basement membranes and, with chronicity, possible permanent changes as the airways become remodeled.

### Diagnostic Approach

The workup of the asthmatic patient should include a thorough history, physical examination, and appropriate laboratory tests to corroborate the physician's clinical impression. Particular emphasis should center on the home setting, work site, occupational exposures, avocational interests, and other possible environmental situations. Asthma is one disease in which identification of the specific (allergic) triggering fac-

tor(s) and subsequent appropriate environmental manipulation to reduce exposure to the allergen burden can have a dramatic impact on the patient's disease process. Likewise, measures to reduce exposure to various indoor pollutants, such as heating fumes, cooking gases, aerosols, and passive smoke, should be incorporated into an asthmatic's avoidance protocol.

The strong association of allergy with asthma mandates an allergic evaluation of all patients who have other than mild and intermittent symptoms. Skin testing to a panel of inhalant aeroallergens relevant to the patient's geographical region provides confirmation of (IgE-mediated) allergic sensitization, which correlates with both the frequency and the severity of the asthmatic's disease. An alternative to skin tests is blood testing (radioallergosorbent testing) for specific IgE against relevant allergens. As with any laboratory test, the findings must be correlated with the clinical history to determine clinical relevance.

### Therapeutic Approach

Successful management of the patient with asthma requires an integrated approach that incorporates patient education, environmental control, the judicious use of an appropriate antiinflammatory therapeutic agent to suppress the underlying inflammatory component, consideration of adjunctive therapy to optimize control, and supplemental use of a bronchodilator to treat breakthrough symptoms. Immunotherapy should be considered in those allergic asthmatic patients who have not responded to environmental and pharmacotherapeutic measures, who have had side effects with the medications, or who have persistent disease because of continuous exposure to relevant aeroallergens throughout the year.

### Patient Education

A successful strategy for manage-

ment of asthma necessitates a partnership between the patient and the healthcare team. Integral to this therapeutic approach is the incorporation of the patient in the development and implementation of any treatment

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participant in the management of his or her disease. This involves helping the patient understand the disease entity, having the patient learn and practice the skills necessary to manage asthma, establishing an open channel of communication for the patient with members of the healthcare team, and developing a joint treatment plan. These aspects cannot be overemphasized, because a disinterested or uninformed patient is likely to foredoom any long-term management plan.<sup>12</sup>

### Environmental Control

Cigarette smoke, aerosol sprays, and cooking odors are important irritants that are capable of triggering an asthmatic's symptoms in the indoor environment. Even more critical to the asthmatic patient is the role of persistent exposure to perennial indoor allergens in inducing a smoldering asthmatic process.

House dust mites, molds, cockroaches, and other insects, as well as

animals are the principal sources that contribute to the indoor allergen burden. Proteinaceous matter from decaying body parts (dust mites, roaches), feces (dust mites, roaches), dander (animals), saliva (cats, roaches), and urinary protein (rodents, cats) represent the major allergen burdens to which the asthmatic is exposed.

Particles less than 10 µm in diameter can easily reach the lower respiratory tract and induce symptoms of asthma. Airtight homes, with their wall-to-wall carpeting, indoor pets, central heating, and ventilation systems are conducive to creating an indoor environment that ensures a patient's exposure to a constant allergen burden. The importance of dust mite control, animal avoidance, and insect eradication cannot be overemphasized, because the asthmatic's disease process can be markedly attenuated or even ablated by incorporation of specific environmental control measures in the household setting.

Pollen allergens are important agents in inducing asthmatic symptoms. Intact pollen grains (eg, ragweed pollen [23 µm diameter]) are too large to reach the lower airways. However, a significant portion of their "total aller-

genic activity" is attributable not only to intact pollen grains but also to pollen fragments (< 10 µm diameter) and microaerosol particles (3 to 7 µm diameter). The relevance of this finding is observed during the pollen season as millions of pollen grains settle to the ground, whereupon dew, rainfall, and humidity extract the relevant protein from the pollen grains, which then becomes airborne in the form of microaerosolized particles. A similar phenomenon occurs with mold, wherein soluble protein from the spores and mycelial elements is dispersed into the atmosphere.<sup>13</sup>

... CONCEPTS IN  
PREVENTIVE THERAPY ...

**Primary Antiinflammatory Agents  
(Primary Controllers)**

Our recognition and understanding of the importance of inflammation in the asthmatic's disease process underscores the importance of using a compound with antiinflammatory properties as a primary therapeutic agent in the management of asthma (Table 1). In this context, early therapeutic intervention should be aimed at suppressing mild but persistent symptoms in an attempt to prevent their escalation into a moderate-to-severe disease process. Currently, inhaled corticosteroids continue to be recognized as the primary antiinflammatory therapeutic agents for controlling asthma. The nonsteroidal antiinflammatory compounds (eg, cromolyn or nedocromil) are alternative choices for the physician. Leukotriene modifiers have secondary antiinflammatory properties, which may enable them to be considered in specific circumstances.

*Inhaled Corticosteroids.* Synthetic corticosteroids that are adapted for inhalation into the lungs have dramatically altered the approach to the treatment of asthma. Their ease of administration and their favorable

**Table 1.** Concepts in Preventive Care

<ul style="list-style-type: none"> <li>• Environmental Control</li> <li>• Primary Antiinflammatory Therapeutic Agents             <ul style="list-style-type: none"> <li>Inhaled corticosteroids</li> <li>Cromolyn/nedocromil</li> </ul> </li> <li>• Adjunctive Controllers             <ul style="list-style-type: none"> <li>Maintenance bronchodilators</li> <li>Long-acting beta<sub>2</sub> agonists</li> <li>Methylxanthines/theophyllines</li> <li>Leukotriene modifiers</li> </ul> </li> <li>• Rescue Bronchodilators             <ul style="list-style-type: none"> <li>Short-acting beta<sub>2</sub> agonists</li> <li>Anticholinergics</li> </ul> </li> <li>• Immunotherapy</li> </ul>
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risk:benefit ratio compared with oral steroids have made them the drug of choice for suppressing asthmatic inflammation.

Inhaled corticosteroids are the most effective therapeutic agents in our arsenal for controlling patients with persistent asthma. The ability to titrate the dosage provides an intervention strategy across the spectrum of asthma severity. Properly controlled clinical trials demonstrate that inhaled corticosteroids improve asthma symptoms, minimize nocturnal awakenings, decrease exacerbations, reduce the need for supplemental short-acting bronchodilator rescue, and improve quality of life. With respect to lung function, the inhaled corticosteroids increase forced expiratory volume in one second (FEV-1), increase peak expiratory flow (PEF), reduce the variability in peak flow, and abrogate the deterioration in long-term survival curves of lung function. With continued use, inhaled corticosteroids also attenuate airway hyperresponsiveness, as measured by provocative models using methacholine, histamine, allergen, cold air, oxygen saturation (SO<sub>2</sub>), exercise, and other pharmacologic stimuli.<sup>14,15</sup>

Several important concepts with respect to the therapeutic action of inhaled corticosteroids should be highlighted. Laitinen and colleagues<sup>16</sup> demonstrated that even milder asthmatics have airway inflammation, as observed from their biopsy studies of 13 asthmatics that showed significant accumulation of eosinophils in the airways of patients who previously used only bronchodilator therapy. Subsequent therapy with an inhaled steroid (budesonide) at a dose of 1200 µg/day resulted in resolution of eosinophilic inflammation, a reduction in basement membrane protein, and restoration of respiratory architecture.

In a 2-year, double-blind, positive-controlled trial that compared budesonide at a dose of 600 µg twice daily

to maintenance therapy with a beta<sub>2</sub>-agonist bronchodilator (terbutaline at 2 puffs bid), Haahtela and colleagues<sup>17</sup> demonstrated that over the initial 2 years of maintenance treatment,

*Inhaled corticosteroids are the most effective therapeutic agents in our arsenal for controlling patients with persistent asthma.*

budesonide reduced asthma symptoms and improved lung function significantly compared with terbutaline. Furthermore, the inhaled corticosteroid therapy significantly dampened airway hyperresponsiveness by approximately 2- to 3-fold, whereas beta<sub>2</sub>-agonist therapy with terbutaline had no appreciable effect on methacholine-induced bronchial hyperresponsiveness.

A similar study by Woolcock and colleagues<sup>18</sup> demonstrated that the inhaled corticosteroid, beclomethasone dipropionate (BDP), shifted airway hyperresponsiveness by approximately one log (10-fold), whereas the control group treated with theophylline showed no effect in this important parameter of airway reactivity. These are critical studies that clearly differentiate the anti-inflammatory properties of inhaled steroids from the classic bronchodilator properties of beta<sub>2</sub> agonists and theophylline compounds.

Furthermore, this raises the question whether early intervention with an antiinflammatory agent is critical for preservation of long-term lung function. The Haahtela study<sup>17</sup> provided evidence that early intervention with an inhaled steroid (budesonide) results both in an improvement in clinical symptoms and lung func-

tion—endpoints that were not achieved in the beta<sub>2</sub> agonist-treated group, even after inhaled steroid therapy was added to their regimen in the 1-year follow-up phase of the study. This surprising observation that a delay in introducing inhaled steroid therapy might mitigate the ability of inadequately treated patients to catchup has become an important issue in asthma management. It is further addressed by the Selroos study, which showed that the longer the interval before introducing steroid therapy in patients with compromised lung function, the less likely the parameters of pulmonary function are to achieve normalcy.<sup>19</sup>

Corticosteroids may act through several different mechanisms, including inhibition of cellular recruitment, arachidonic acid metabolism, and mediator synthesis; restoration of beta<sub>2</sub>-receptor responsivity; and down regulation of the effects of various inflammatory mediators on their target sites. The clinical relevance of these findings is demonstrated in properly performed provocation studies, which show that inhaled corticosteroids, given for an adequate length of time, block the late phase of a (specific) allergen-induced challenge, indirectly diminish the early challenge response, reduce airway inflammation, and inhibit development of nonspecific airway reactivity. Chronic administration results in a decrease in airway hyperresponsiveness to both specific (allergen) and nonspecific (irritant) stimuli.<sup>20,21</sup>

The research and development teams of the various pharmaceutical corporations have developed the newer corticosteroid preparations to capitalize on design methods that increase potency, improve the therapeutic index, and facilitate easy breakdown of the molecule to improve the safety index. Halogenation (ie, chemical addition of a chlorine or a fluorine molecule at specific carbon sites on the basic steroid mol-

ecule) further increases the therapeutic activity (potency) of the specific compound. Esterification results in more rapid breakdown of the corticosteroid molecule by the liver (first-pass effect) and thereby reduces the systemic bioavailability.

There are presently 5 inhaled corticosteroid preparations on the US market, and a sixth preparation (mometasone furoate) is in phase III clinical trials. The dose comparability among the various inhaled corticosteroid preparations is a difficult issue to address (Table 2). Studies of tissue receptor binding affinity allow stratification of the inhaled (topical) corticosteroid preparations into high-, moderate-, and low-potency preparations. These studies demonstrate that mometasone furoate (20:1) and fluticasone propionate (18:1) have the highest potency when compared with dexamethasone. The next tier of drugs is represented by budesonide (9:1) and BDP, which is metabolized from dipropionate to monopropionate (9:1), whereas triamcinolone acetonide (3.6:1) and flunisolide (1.8:1) are low-potency preparations. This necessitated giving the lower-potency formulations at greater strengths (ie, 200 to 250 mcg/puff) to achieve the same response as BDP in challenge models or clinical endpoints.<sup>22-24</sup>

Equally important to this equation are the dynamics of inspiratory flow and particle distribution, which are both critical factors in corticosteroid deposition in the lower airways. The new dry powder formulations (budesonide [Pulmicort Turbuhaler], fluticasone [Flovent Diskus]) result in improved delivery of respiratory particles at a more optimal particle size (3- to 7- $\mu$ m diameter particles) that more easily reach the respirable portion of the bronchial tree.

The complicated aspects of this become apparent when the difficulty of achieving adequate therapeutic control with the older low-potency corticosteroid preparations is recog-

nized. For example, in a patient requiring 1000 µg/day of BDP (5 puffs 4 times per day) the likelihood of patient noncompliance with such a regimen, as well as the poor reproducibility of inspiratory rates with such frequent repetitive inhalations, accentuates the therapeutic problem.

The clinical implications of these differences in pharmacokinetics between the various inhaled corticosteroid preparations have been difficult to assess because of the relatively flat dose-response curve with inhaled steroids. However, based on recent carefully designed clinical trials measuring various relevant clinical endpoints (symptoms, PEF, and FEV-1), there is a general consensus that fluticasone (metered dose inhaler [MDI] [2:1]) and budesonide (1.3-1.5:1) are more potent than BDP.<sup>24</sup> A study involving fluticasone in its dry powder diskhaler formulation (1.5:1) showed it to be more potent on a nominal dose basis (µg/µg) than triamcinolone (MDI used with a spacer).<sup>24</sup> In controlled trials, the fluticasone Diskus appears to behave similarly to the other fluticasone preparations. In this context, the new higher-potency corticosteroid preparations result in better therapeutic control with lower total dose requirements. Furthermore, control can be accomplished in a more user-friendly way, with a once- or twice-daily maintenance regimen that significantly improves patient compliance (risk benefit:ratio).

In symptomatic patients, judicious adherence to the treatment regimen is necessary, starting with an initial dose that is adequate to bring symptoms under control and tapered as tolerated to the lowest effective dose that sustains symptom control during the maintenance phase of therapy. This dose must be adequate to suppress the underlying inflammatory component, improve pulmonary function, and reduce the frequency and severity of symp-

toms. Subsequent adjustments in dosage (step up or step down) can be made based on assessment of clinical symptoms and peak expiratory flow rates.

The NHLBI guidelines have provided clinicians with information on therapeutic dosing considerations with inhaled corticosteroids, based on the severity of a patient's disease. With this in mind, a reasonable approach to control mild (200 to 400 µg/day), moderate (400 to 800 µg/day), and severe asthma (> 800 µg/day) can be constructed. Implicit in these suggestions is the importance of beginning therapy with a maximal recommended dose over the first 1 to 2 weeks to bring the inflammatory process under control quickly (800 to 1600 µg/day) and then to reduce this amount to the lowest dose that still provides adequate therapeutic control (~200 to 800 µg/day).<sup>1,25</sup>

The new inhaled corticosteroid preparations have markedly improved the risk:benefit ratio of steroid therapy compared with chronic oral prednisone therapy, which is saddled with a significant potential adverse-event profile that includes adrenal suppression, bone demineralization, growth suppress-

**Table 2.** Inhaled Corticosteroid Preparations

Compound	Dose/Actuation (µg)	Typical Dosage	Total Dose (µg)
Beclomethasone	42	2-4 p qid	168-672
Flunisolide	250	2-4 p bid	1000-2000
Triamcinolone	(200) 100	2-4 p bid	800-1600
Budesonide	200	2-4 p bid	200-1600
Fluticasone	44/110/220	1-2 p bid	88-880
Mometasone*	200/400	1-2 p bid	200-800

\*Not yet approved in the United States. p = puffs.

sion, ocular complications, and local effects in the oral pharynx and the skin. Serious adverse events are uncommon with the inhaled (topical) preparations but the risk for adverse events correlates with the total daily dose.<sup>26-29</sup> The degree of risk can be minimized by the use of the newer higher-potency steroids, where smaller total daily doses are required to maintain therapeutic control. This measure reiterates the philosophy of step-down therapy in which patients are maintained on the lowest dose that still provides clinically beneficial therapeutic control.

*Cromolyn.* Cromolyn sodium (Intal) is a derivative of a naturally occurring antispasmodic extracted from a Mediterranean weed. Cromolyn sodium has been demonstrated to be clinically efficacious in the management of seasonal allergic asthma, perennial allergic asthma, exercise-induced asthma, occupational asthma, and certain types of irritant-induced asthma. Its mechanisms are not completely understood, but it appears that one of its actions may be to stabilize the membranes of a variety of cells (eg, mast cells, sensory nerve cells) involved in the inflammatory cascade, resulting in the inhibition of inflammatory mediator release. It also has been shown to interfere with the migration of eosinophils to the inflammatory site and to decrease the number of eosinophils and the concentration of eosinophilic inflammatory mediators (eg, eosinophil cationic protein) in the bronchial lavage fluids of treated asthmatics.<sup>30</sup>

The most successful therapeutic approach with cromolyn is to use the drug prophylactically, beginning 7 to 10 days before the allergen season. Based on cromolyn's remarkable safety profile, an aggressive approach to treatment can be pursued, with an initial inhaled dose of 2 puffs 4 times daily (6400 µg) being

recommended. Obviously, this necessitates patient compliance, but with a motivated patient who is instructed in the requirement of using the drug diligently in this early treatment period, it may be possible to reduce this dosage to a 2 to 3 times daily regimen for maintenance control.

In symptomatic patients it is even more important to emphasize aggressive dosing of the drug, because it may be necessary to double the dose from 2 to 4 puffs 4 times daily during the first several weeks of therapy to achieve control. Once control is attained, it may be possible to taper the dosage to a more user-friendly regimen that ensures patient compliance.

Clinical studies demonstrate that cromolyn-treated patients receiving 6400 µg per day (2 puffs 4 times daily) show improvement in overall asthma symptoms (daytime asthma, nocturnal asthma, and cough) and parameters of lung function (PEF, spirometry) airway hyperreactivity, and the need for supplemental bronchodilators. Comparative studies show cromolyn to be comparable to lower-dose inhaled steroid therapy in the management of asthma. However, the combination of cromolyn with a beta<sub>2</sub> agonist has been shown to result in better symptom control than cromolyn alone. Although theophylline provides a similar clinical benefit, the low frequency of adverse effects associated with cromolyn represents a significant therapeutic advantage.<sup>31,32</sup>

The use of a spacer can further improve both drug delivery and clinical response in patients, and a strong case can be made to employ a spacer in all cases in which inhaled cromolyn is prescribed. Likewise, the nebulized formulation of cromolyn can be used to maintain therapeutic levels when a MDI cannot be continued. This is particularly useful in cases involving young children who cannot learn the

correct MDI technique during periods of severe lower airway inflammation (eg, bronchitis or respiratory infection) that make an aerosol intolerable or when intolerance to the aerosol propellant is a factor.

*Nedocromil.* Nedocromil sodium (Tilade) is a nonsteroidal antiinflammatory compound that is classified as a pyranoquinoline. It is a synthetically derived dicarboxylic acid with a tricyclic ring backbone. These synthetic alterations have resulted in a compound with a broader spectrum of anti-inflammatory activity compared with cromolyn. Studies have demonstrated that nedocromil has activity on a variety of cell types that are involved in the asthmatic cascade (eg, eosinophils, neutrophils, epithelial cells, mast cells); inhibits inflammatory mediator release; and has a modulatory effect on neural pathways, with implications for both the immediate and late phases of the asthmatic's clinical response. Clinical studies have demonstrated nedocromil's efficacy in seasonal and perennial asthma, cold air-induced, SO<sub>2</sub>-induced, exercise-induced, and cough-variant asthma.<sup>33</sup>

In studies that use bronchoprovocation, nedocromil appears to be comparable to low-dose BDP in reducing the underlying bronchial hyperresponsiveness of patients with mild-to-moderate asthma. In this context, one of the more clinically relevant features of airway inflammation is heightened diurnal variability in PEF. Nedocromil has been shown to both attenuate this diurnal flux and improve overall lung function (eg, FEV-1, PEF) when used on a regular daily basis.<sup>34</sup>

In contrast, maintenance therapy with a short-acting beta<sub>2</sub> agonist (eg, albuterol) neither results in a sustained improvement in PEF nor a reduction in the diurnal variability in peak flow. The relevance of this may be correlated with bronchoalveolar lavage studies, which

show that nedocromil inhibits the influx of inflammatory cells (eg, eosinophils) into the lungs, whereas a bronchodilator (eg, albuterol) does not.

*Clinical studies have demonstrated nedocromil's efficacy in seasonal and perennial asthma, cold air-induced, SO<sub>2</sub>-induced, exercise-induced, and cough-variant asthma.<sup>33</sup>*

In contrast to cromolyn, nedocromil given in a dose of 2 puffs (4 mg) 4 times daily results in an improvement in asthma symptoms within days of initiating therapy. For optimal control, the drug should be initiated at a dose of 2 puffs 4 times daily for the first 1 to 2 weeks of therapy to ensure suppression of bronchial hyperresponsiveness, improve lung function, and reduce symptoms. Once control is established, the dose of the drug should be reduced to a twice-a-day maintenance regimen of 2 to 4 puffs to sustain control.<sup>35-37</sup>

For chronic maintenance therapy, studies show that nedocromil, 4 mg 4 times daily, is comparable to low-dose inhaled corticosteroids (BDP ≤ 400 µg per day) and superior to maintenance bronchodilator therapy (albuterol, 2 puffs 4 times daily) in reducing daytime-nocturnal asthma, wheezing, shortness of breath, and/or cough. When added to maintenance theophylline (400 to 800 µg per day) nedocromil has been shown to result in further improvement in clinical symptoms and an ability to reduce and/or replace theophylline with no loss of therapeutic effectiveness. Various studies have shown an added benefit when nedocromil is added to a

maintenance regimen of theophylline, beta<sub>2</sub> agonists, and inhaled corticosteroids. This may be particularly beneficial in allowing patients with moderate-to-severe asthma to reduce their total inhaled steroid requirements and yet maintain control.<sup>38</sup>

In direct comparison studies, nedocromil appears to be comparable to cromolyn in improving the asthmatic symptoms of patients with predominantly allergic asthma, but it is superior to cromolyn in treating predominantly nonallergic asthmatics.<sup>39</sup>

In summary, nedocromil appears to represent a therapeutic agent with a broader spectrum of activity than cromolyn and, most importantly, it is a compound that can be reduced to a twice-a-day maintenance dosage for effective control. Its ease of administration and safety make nedocromil a reasonable choice for use in patients with mild-to-early moderate asthma.

#### **Adjunctive Controllers**

The principal use of these therapeutic compounds is as adjunctive therapy to a primary antiinflammatory therapeutic agent to further optimize asthma control. Some of these compounds provide long-lasting bronchodilation (salmeterol [SMT], theophylline), whereas the leukotriene modifiers and to a lesser extent the theophylline compounds have secondary antiinflammatory properties.

*Maintenance Bronchodilators.* The introduction of salmeterol (Serevent) has provided the option of using this long-acting beta<sub>2</sub> sympathomimetic drug for maintenance control of asthma and prevention of bronchospasm, control of nocturnal asthma, and prevention of exercise-induced asthma.<sup>40-42</sup> The principal positioning of this therapeutic agent is in patients who are already maintained on a primary antiinflammatory drug for whom the

addition of a maintenance bronchodilator would optimize control. In this context, the addition of salmeterol could obviate the need for increasing the corticosteroid dose in a less than optimally controlled patient, thereby improving the risk:benefit ratio of the total drug therapy regimen.

Salmeterol is also an appropriate therapeutic choice for control of nocturnal asthma, where the longer duration of action would provide reasonable control for the majority of patients. In contrast, short-acting bronchodilators (3- to 4-hour duration) would not be expected to provide an adequate length of coverage through the evening hours. Salmeterol would also be a superior choice in patients who have gastroesophageal reflux in which the use of theophylline would further aggravate lower esophageal sphincter pressure and result in worsening reflux. A final indication for salmeterol is in exercise-induced asthma. Because of its longer duration of action, this drug may provide protection against several different exercise events during a 10- to 12-hour period.

Salmeterol is available both in an MDI formulation (42 µg per puff), which is recommended at a dose of 1 to 2 puffs twice a day, as well as a dry powder inhalation device (50 µg per puff) administered as 1 inhalation twice daily. Patients should be cautioned not to exceed a twice-daily dosing frequency, because the prolonged half-life of the drug may result in an exaggerated pharmacologic response involving tremor, muscle cramps, headache, or adverse cardiovascular events. Furthermore, salmeterol should never be used to relieve acute symptoms of bronchospasm.<sup>42</sup> A short-acting selective beta<sub>2</sub> agent should be used for relief of breakthrough symptoms in a patient who is already on maintenance therapy with salmeterol.

Theophylline therapy has been a cornerstone of asthma treatment through the years. As with beta-adrenergic sympathomimetic agents, theophylline appears to exert its primary influence through relaxation of smooth muscle of the bronchial tree. It inhibits the breakdown of the enzyme phosphodiesterase, which leads to an increase in cyclic adenosine monophosphate (cAMP) concentrations, thereby resulting in smooth muscle cell relaxation.<sup>42</sup>

As emphasized, our current approach to the treatment of asthma involves the aggressive use of an inhaled preventive therapeutic agent. As a result, theophylline is now viewed as an adjunctive, albeit important, therapeutic agent in asthmatic patients whose condition is not easily controlled by the use of inhaled nedocromil or inhaled corticosteroids supplemented by an inhaled beta<sub>2</sub>-selective sympathomimetic agent. This current strategy reflects not only the superior antiinflammatory properties of these preventive inhaled agents but also the toxic effects associated with theophylline therapy.

In view of the small margin between therapeutic effects and toxicity, individualization of dose is mandatory with theophylline therapy. The use of sustained-release long-acting (once or twice daily) preparations has improved this aspect of care, because of the more consistent theophylline release characteristics, which provide a more consistent plasma concentration with less marked peak:trough variation. In this regard, it is important not to switch to using various preparations, because significant differences in serum blood levels may result from the differences in absorption characteristics among preparations from different manufacturers.

The once-a-day sustained-release products may be most useful in the

subset of asthmatics with nocturnal symptoms who otherwise find it difficult to sleep through the night because of the short duration of activity of classic sympathomimetic agents. However, this consideration

*As emphasized, our current approach to the treatment of asthma involves the aggressive use of an inhaled preventive therapeutic agent.*

must be counterbalanced by the possibility of increased reflux resulting from a reduction in lower esophageal pressure with theophyllines.

*Leukotriene Modifiers.* The sulfido-peptide leukotrienes (LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>) are potent inflammatory molecules that are elaborated by mast cells, basophils, eosinophils, and a variety of other cells. As a result, these molecules play a role in both the mast cell-driven (acute) asthmatic reaction as well as in the T cell-orchestrated (chronic) inflammatory process, in which secondary inflammatory cells (eg, eosinophils, basophils) predominate. These molecules alter vascular permeability, contribute to airway edema, and enhance mucus production. The leukotriene LTD<sub>4</sub> has been shown to be the most potent bronchoconstrictor in man; it is 1000 times stronger than histamine in inducing bronchial constriction. Therefore, the leukotrienes are potent mediators of bronchoconstriction and inflammation and appear to be integral to the asthmatic process.<sup>43,44</sup>

Several therapeutic approaches have been taken to manipulate the 5-lipoxygenase pathway of the arachi-

donic acid cascade, including targeting the development of a 5-lipoxygenase enzyme inhibitor (zileuton), and the development of specific leukotriene receptor antagonists (zafirlukast, montelukast). Mechanistic studies with these compounds have demonstrated their ability to inhibit allergen-induced early- and late-phase airway responses, histamine-induced responsiveness postallergen challenge, and inflammatory cell recruitment. Furthermore, attenuation of exercise-induced and sulfur dioxide-induced effects on the airways have also been demonstrated in appropriately designed challenge models.<sup>43,44</sup>

These specific leukotriene receptor antagonists have gained favor in the treatment of mild- to moderate-persistent asthma, based on their ease of dosing (oral) and their approval for use in children. Clinical trials with these agents have demonstrated an improvement in asthma symptoms and a reduction in exacerbations and a need for rescue bronchodilator therapy. Furthermore, these agents demonstrate both an immediate bronchodilator effect (eg, FEV-1 increased 10% to 15% compared with baseline) and a sustained clinical improvement with chronic maintenance therapy.<sup>45-47</sup>

Comparative studies demonstrate the clinical benefit of leukotriene modifiers to be comparable to that achieved with either cromolyn or nedocromil and theophyllines.<sup>48</sup> Furthermore, they appear to be comparable to low-dose inhaled steroids (eg, BDP) but do not exhibit the dose-response profile that could be achieved with inhaled steroid therapy. Studies of comparable asthmatic patient populations suggest that appropriate doses of inhaled steroids will result in an approximately 2-fold differentiation of inhaled steroids versus leukotriene modifiers with respect to either

symptom improvement or lung function (versus placebo).

Consideration of leukotriene modifiers as adjunctive therapy is particularly appealing, based on trials demonstrating their ability to reduce acute exacerbations and inhaled steroid requirements and to augment the clinical response in patients who are not adequately controlled by inhaled steroids. With respect to add-on therapy, comparative trials have again demonstrated that the long-acting bronchodilator salmeterol improves FEV-1 about 2-fold greater than either zafirlukast or montelukast. However, when examining other aspects of total asthma control (eg, rate of exacerbations, need for supplemental rescue medications, and specific parameters of quality of life), these differences are of a lesser magnitude.<sup>49,50</sup>

In summary, the leukotriene modifiers are most appropriately used as add-on therapy for patients who have not achieved adequate control using a primary antiinflammatory therapeutic regimen. In carefully selected patients, these agents may also be considered an alternative to inhaled steroid therapy when considerations of compliance, age, or safety impact on the choice of a first-line agent. However, caution must be exercised in this decision process because evidence is still lacking that leukotriene modifiers can significantly alter airway inflammation in patients with chronic (persistent) asthma. By contrast, inhaled corticosteroids clearly have been shown to reduce airway inflammation in biopsy studies of asthmatics. Certainly, early intervention with the agent best capable of arresting or suppressing the underlying airway inflammation would be most likely to result in improvement in clinical symptoms and in long-term lung function.

### Concurrent Therapy

Our understanding of the asthmatic disease process has advanced

immeasurably through the technical advances of bronchoscopy and biopsy coupled with the molecular and immunologic advances in the basic science laboratory. We now recognize airway inflammation as the “subsoil” for the development of abnormal airway physiology, heightened bronchial responsiveness, and chronic asthmatic symptomology. However, this must be balanced with our observations that smooth muscle dysfunction with its resultant bronchoconstriction is the hallmark of the disease for the patient.

Although antiinflammatory therapy reduces the airway hyperresponsiveness that contributes to bronchoconstriction, it does not eliminate it. This would suggest that treatment of both components of the asthmatic disease—the underlying airway inflammation and the bronchoconstriction—are necessary to achieve optimal asthma control. In fact, concurrent therapy with an inhaled corticosteroid and an inhaled long-acting beta<sub>2</sub> agonist has been shown to result in superior asthma control compared with either inhaled corticosteroids plus leukotriene modifiers, inhaled corticosteroids plus theophylline, or higher doses of inhaled corticosteroids alone.<sup>38</sup>

The methodology of bronchoprovocation enables the characterization of these 2 critical components of the asthmatic process. In this model, it can be shown that the early-phase response to allergen provocation can be blocked by pretreating with a beta<sub>2</sub> agonist. However, this treatment has no effect on the subsequent late-phase response of asthma. In contrast, treatment with an inhaled corticosteroid prevents the late-phase response but only partially mitigates the acute airway reactivity.<sup>51</sup> These constructs would provide a logical basis for a dual-component therapeutic regimen, which addresses both the early-phase and late-phase asthmatic components.

Furthermore, data are beginning to show the interrelationships between airway inflammation and airway smooth muscle function. In this context, persistent airway inflammation can significantly contribute to bronchial hyperresponsiveness, which in turn leads to bronchoconstriction. Interestingly, airway smooth muscle has also been shown to be capable of releasing inflammatory mediators, which may contribute to increased inflammation in the airway.<sup>51-53</sup>

These observations have several important implications with respect to treatment with long-acting beta<sub>2</sub> agonists. On the one hand these beta<sub>2</sub>-agonist compounds have obvious bronchodilating properties through stimulation of beta<sub>2</sub>-adrenergic receptors in the lung, which leads to increased production of cAMP. cAMP induces a sequence of intracellular events that lead to relaxation of airway smooth muscle (bronchodilation).<sup>54</sup> Furthermore, long-acting beta<sub>2</sub>-agonist drugs also have non-bronchodilatory effects, which may have clinical relevance.

In-vitro studies have demonstrated that inhaled long-acting beta<sub>2</sub>-agonist drugs can alter cell adhesion, thereby reducing white blood cell accumulation in the airways; inhibit mast cell inflammatory mediator release; increase ciliary beat; improve mucociliary clearance; and decrease airway edema.<sup>55-58</sup>

In addition, recent in-vitro studies suggest that the inhaled long-acting beta<sub>2</sub> agonists may prime inactive glucocorticoid receptors, thereby enhancing the effects of inhaled corticosteroids and making it easier for the primed receptors to be activated by corticosteroids. In effect, this may explain why a lower dose of an inhaled steroid is effective when it is combined with an inhaled beta<sub>2</sub>-agonist agent as compared with the requirements for a much higher dose of an inhaled corticosteroid alone.<sup>59-61</sup>

This reciprocal relationship is emphasized in studies that have shown that inhaled corticosteroids may enhance the effects of inhaled long-acting beta<sub>2</sub> agonists.<sup>20,62</sup> Specifically, corticosteroids appear to increase the number of available beta<sub>2</sub> receptors as well as heighten their sensitivity to beta<sub>2</sub> agonists.

A recent study by Sue-Chu and colleagues provides further support for the complementary effects of inhaled corticosteroids and long-acting beta<sub>2</sub> agonists in controlling airway inflam-

mation in patients with asthma. This double-blind bronchial biopsy study demonstrated that treatment with concurrent therapy (fluticasone 200 µg twice daily + SMT 50 µg twice daily for 12 weeks) resulted in decreases in CD3<sup>+</sup>, CD4<sup>+</sup>, and CD25<sup>+</sup> lymphocytes that were similar to or greater than those observed with higher doses of fluticasone alone (fluticasone 500 µg bid). Furthermore, concurrent therapy resulted in a significant reduction in the number of mast cells when compared with either fluticasone alone at either the 200- or the 500-µg dose.<sup>63</sup>

Several pivotal trials with BDP established the concept that a long-acting bronchodilator (eg, SMT) could be added to a low dose of an inhaled corticosteroid and exert similar if not greater improvement in lung function than doubling the inhaled corticosteroid dose alone.

Specifically, these findings can be highlighted in the study by Murray and colleagues (Table 3).<sup>66</sup> In this trial, 514 adult asthmatics who were symptomatic despite inhaled corticosteroid therapy were studied. In this randomized, double-blind, parallel group, multicenter trial, the addition of salmeterol (21 µg/puff [2 puffs bid]) to low-dose BDP (42 µg/puff [2 puffs bid]) provided greater improvement in lung function than doubling the BDP alone (336 µg bid). The improvement in FEV-1 (BDP/SMT: 3 mL; Double BDP: 170 mL) was paralleled by a similar improvement in AM PEF (49 L/mm versus 31 L/mm increase), PM PEF (40 L/mm versus 24 L/mm increase), reduction in asthma symptoms ( $P < 0.05$ ), and reduction in or the need for supplemental albuterol ( $P < 0.05$ ).

Similarly designed studies have been performed with fluticasone to which salmeterol has been added (Table 4).<sup>67-70</sup> Condemi and colleagues<sup>67</sup> studied 437 asthmatics, age 12 years old and older, who remained symptomatic despite receiving fluti-

**Table 3.** Asthmatics Symptomatic Despite Inhaled Corticosteroid Therapy

Investigator	Patients	Duration, Weeks	Lung Function	Symptoms	Albuterol
Greening	426	24	↑	↓	↓
Woolcock	738	24	↑	↓	↓
Kelsen	483	24	↑	↓	↓
Murray	514	24	↑	↓	↓

Source: References 64, 18, 65, 66.

**Table 4.** Asthmatics Symptomatic Despite Receiving Fluticasone Alone

Investigator	Patients	Duration, Weeks	Lung Function	Symptoms	Albuterol
Condemi	437	24	↑	↓	↓
Baraniuk	680	12	↑	↓, =	↓
Pearlman	136	4	↑	↓, =	↓
Van Noord	274	12	↑	↓	↓

Source: References 67, 68, 69, 70.

casone (44 µg/puff [2 puffs bid]) for 2 to 4 weeks. This was a randomized, double-blind, parallel group, 24-week, multicenter trial, in which patients either had their fluticasone dose more than doubled (220 µg bid) or were randomized to continued low-dose fluticasone (88 µg bid) to which SMT 2 puffs bid was added. The patient group receiving fluticasone plus SMT demonstrated a significantly greater improvement in lung function as opposed to the fluticasone alone group (FEV-1 (increase) 430 mL versus 330 mL [ $P = 0.013$ ]). Parallel increases were observed in AM PEF (47 L/min versus 24 L/min increase,  $P < 0.001$ ). Similarly, statistically significant improvements were observed in asthma symptoms, nocturnal awakening (-0.22 versus 0.11,  $P < 0.001$ ), and supplemental albuterol use (-2.5 puffs versus -1.6 puffs,  $P < 0.001$ ).

Baraniuk and associates<sup>68</sup> studied 680 patients, 12 years of age and older, who remained symptomatic despite low-dose inhaled corticosteroid therapy. This was a randomized, double-blind, triple-dummy, multicenter trial that compared medium-dose fluticasone therapy (440 µg/day) to medium-dose triamcinolone therapy (1200 µg/day) to dual therapy with low-dose fluticasone (168 µg/day) and SMT (84 µg/day). In this trial, low-dose fluticasone plus SMT was statistically superior to therapy with either medium-dose fluticasone (FEV-1/supplemental albuterol) or medium-dose triamcinolone (FEV-1/AM PEF/PM PEF/nocturnal awakenings/overall asthma symptom scores/albuterol use).

Our concept of asthma has now evolved to recognizing that both the undercurrent of inflammation as well as the clinical component of bronchoconstriction are part and parcel of the disease. Therefore, for many patients with more moderate-to-per-

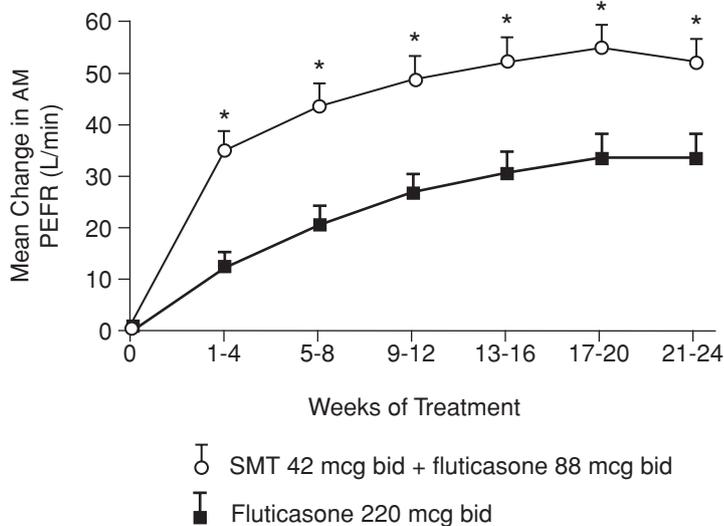
sistent asthma the decision becomes which combination of medications to use to achieve optimal control. This has led to the recognition that a therapeutic product that combines both a primary antiinflammatory agent (eg, an inhaled steroid) with a long-acting bronchodilator would be valuable. This type of preparation would combine 2 agents that would complement each other in terms of their therapeutic actions. Certainly, a significant patient population exists that would benefit from concurrent therapy. However, for FDA approval, studies must ascertain that each component contributes to the claimed effect and that the dosage of each component in the combination is demonstrated to be both safe and effective.

Studies in North America and Europe have been carried out with the combination product of fluticasone plus salmeterol (Advair) and studies are currently under way in Europe with the combination product of budesonide and formoterol (Symbicort). The following is a review of the recently FDA-approved fluticasone/SMT combination product.

The pivotal studies with the fluticasone/SMT combination product have been carried out at 3 separate dosage strengths: fluticasone (100 µg)/salmeterol (50 µg), fluticasone (250 µg)/salmeterol (50 µg), and fluticasone (500 µg)/salmeterol (50 µg). Both primary measures of efficacy (survival curve—probability of remaining in the study without withdrawing because of worsening asthma and pulmonary function—as well as secondary measures of efficacy—PEF/asthma symptoms/nocturnal asthma/rescue albuterol use/quality of life) have been demonstrated to be positively affected by use of the combination products (Figures 2 and 3).<sup>71-73</sup>

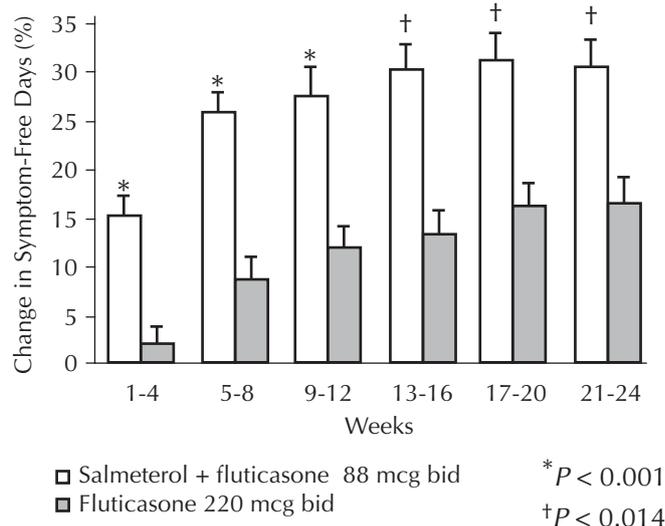
The studies were designed to stratify patients requiring low-dose steroid therapy (100/50 µg), moderate-dose

**Figure 2.** Morning Peak Expiratory Flow After Treatment With Combination Therapy



\* $P < 0.001$ ; PEF = peak expiratory flow rate; SMT = salmeterol. Source: Condem J, Goldstein S, Kahlberg C, et al. The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. *Ann Allergy Asthma Immunol*; 1999;82:383-389. Reprinted with permission from the American Medical Association.

**Figure 3.** Percent of Days With No Asthma Symptoms



\* $P < 0.001$ ; PEF = peak expiratory flow rate. Source: Condem J, Goldstein S, Kahlberg C, et al. The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. *Ann Allergy Asthma Immunol*; 1999;82:383-389. Reprinted with permission from the American Medical Association.

steroid therapy (250/50  $\mu\text{g}$ ), and high-dose steroid therapy (500/50  $\mu\text{g}$ ). The former 2 studies, 100/50 and 250/50, were placebo-controlled trials, whereas the latter study, 500/50, was a positive control study comparing the combination product with concomitant therapy using fluticasone and SMT.<sup>71-73</sup>

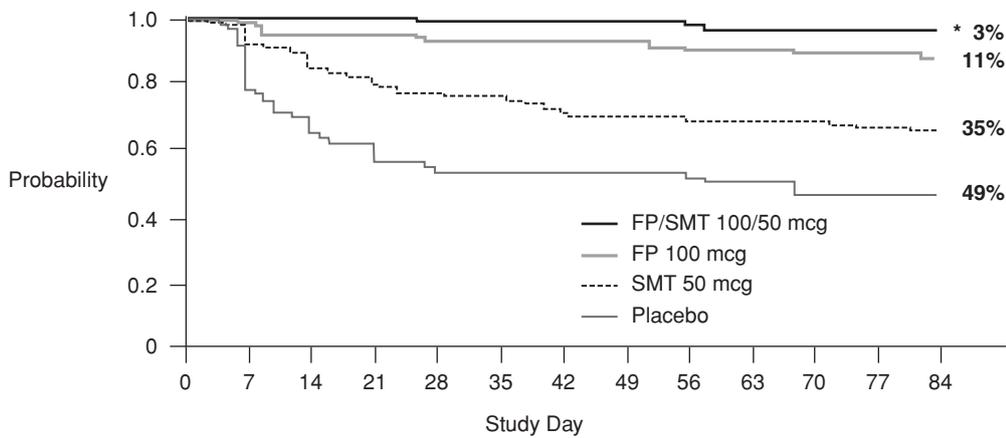
In both placebo-controlled trials perhaps the most striking observation came from the survival curves where less than 3% and 4% of patients, respectively, on the combination product were withdrawn because of worsening asthma (Figure 4). These findings were significantly different from those of either treatment with the inhaled steroid alone, the long-acting bronchodilator, or placebo. Furthermore, with respect to improvement in lung function, the combination product demonstrated in both the milder asthmatic population and in the more moderate asthmatic group a significant improvement compared with either drug alone or placebo (Figure 5). In this respect, a remarkable 500-mL improvement in FEV-1 was observed with the combination product in both study populations.<sup>71,72</sup>

In the more severe asthmatic study population, the high-dose combination product (500/50) was equal to if not superior to concurrent therapy, again demonstrating an additive, if not augmentative, effect from administering the combination drug compared with using the 2 individual agents together or with high-dose steroid therapy alone.<sup>73</sup>

An interesting corollary to these clinical findings is recent laboratory data demonstrating that SMT appears capable of upregulating steroid receptors.<sup>59</sup> Previous data have shown that corticosteroid therapy can upregulate beta-receptor subsensitivity.<sup>20,62</sup> These complementary mechanistic actions may help explain the augmentative therapeutic response observed when these agents are used in combination.

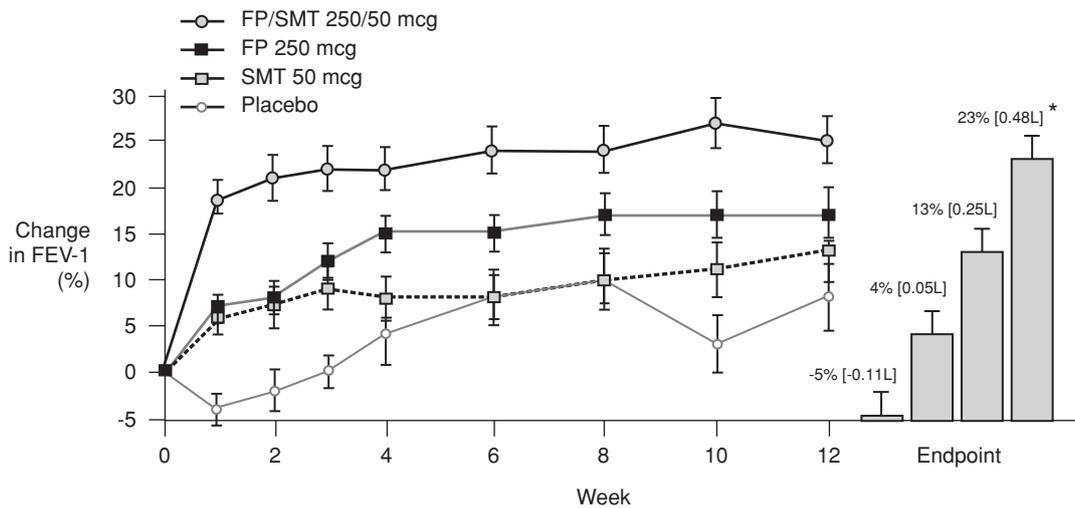
In summary, the approach to treating asthma with a fixed combination

**Figure 4.** Percentage of Patients Withdrawn From Trials For Worsening Asthma



\*Differs from FP 100 mcg, SMT, placebo,  $P \leq 0.020$ . FP = fluticasone propionate; SMT = salmeterol.  
 Source: Kavuru M, Melamed J, Gross G, et al. Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma: A randomized, double-blind, placebo controlled trial. *J Allergy Clin Immunol* 2000;104:1108-1116. Reprinted with permission.

**Figure 5.** Combination Product and Its Effect on Asthma Symptoms



\*Differs from FP 250 mcg, SMT, placebo at endpoint  $P \leq 0.003$ . FP = fluticasone propionate; SMT = salmeterol.  
 Source: Shapiro G, Lumry W, Wolfe J, et al. Combined salmeterol 50 mcg and fluticasone propionate 250 mcg in the DISKUS device for the treatment of asthma. *Am J Respir Crit Care Med* 2000;161:527-534. Reprinted with permission.

product that incorporates an inhaled corticosteroid combined with a long-acting maintenance bronchodilator is particularly attractive, both with respect to patient compliance and in terms of beneficial therapeutic effects. The complementary modes of action of these 2 agents has been demonstrated to result in superior therapeutic control, with improvement in clinical symptoms, reduction in exacerbations, less need for supplemental rescue medication, improved quality of life, improved and maintained lung function, and suppression of bronchial hyperresponsiveness. Neither tachyphylaxis nor masking of asthma exacerbations has been observed with the administration of the combination product.<sup>74,75</sup>

Perhaps the most relevant question to address next is whether patients with milder but persistent asthma would be better managed by the use of a combination product that incorporates 2 drug entities that have complementary actions to control the asthmatic disease process compared with the current stepwise add-on therapeutic approach.

### **Rescue Bronchodilator Therapy**

Preventive therapy is the desirable approach to the management of asthma. However, sympathomimetic bronchodilators are important adjunctive medications for relief of acute symptoms or for the treatment of breakthrough symptoms in a patient who is already on maintenance controller therapy.

In essence, the need for bronchodilator use should be considered an early warning signal for the asthmatic; that is, if a patient's asthma symptoms begin to increase in frequency or if the patient begins to note the need for a bronchodilator on a more frequent basis (> 3 days in a week), it should be an indication of worsening asthma. Steps should then be taken to identify the basis for the worsening of the asthmatic condition. In a patient who is not already on

a primary antiinflammatory agent, this would be an indication that such a drug should be started. If a patient is already on a primary antiinflammatory agent, then the dosage of that compound should be doubled. Subsequent adjustment of the medication regimen should be based on the therapeutic response to these initial manipulations.

*Short-Acting Selective Beta<sub>2</sub> Agonists.* Sympathomimetic bronchodilators have become a mainstay in the therapeutic approach to the treatment of asthma. These agents are the drugs of choice for relief of acute bronchospasm. They are used effectively for the treatment of mild or intermittent asthma symptoms, and they are also effective in preventing or reversing exercise-induced asthma. Improved beta<sub>2</sub> selectivity and increased duration of action are seen with the majority of the noncatecholamine derivatives.<sup>54</sup>

The therapeutic effects of beta-adrenergic agents include bronchodilation as a result of activation of a cell membrane's adenylate cyclase enzyme, which converts adenosine triphosphate to cAMP, resulting in sequestration of intracellular calcium. This leads to relaxation of smooth muscle; increased ciliary movement, which should improve clearance of secretions; and stabilizing effects on the mast cell to decrease mediator release. However, provocation studies demonstrate that beta-adrenergic agents can effectively ablate the immediate asthmatic response but have no demonstrable clinical effect on the late phase of airway reactivity.<sup>54</sup>

Selective beta<sub>2</sub> agonists provide better bronchodilation than the theophylline products in both the acute and chronic state. Furthermore, the addition of aminophylline to a maximum dose of inhaled beta-agonist therapy provides no further improvement in the bronchodilator response. However, in chronic therapy, receptor subsensitivity may develop. This has

led to considerable discussion as to whether these agents should be administered on a regular (4 times daily) maintenance dosage schedule, which again reinforces the suggestion that a short-acting beta<sub>2</sub> agent should be used on an as-needed basis for relief of acute symptoms. Typical dosing is 1 to 2 puffs every 4 to 6 hours, because it is needed for relief of breakthrough asthma symptoms. However, these drugs should not be overused. Increased need for these drugs should signal the need to address the underlying trigger of the asthmatic exacerbation and make appropriate adjustments in the patient's primary antiinflammatory regimen.

Proper administration of the aerosol should be emphasized. Careful demonstration of inhaler technique by the physician, nurse, or patient educator is mandatory and often requires repeated reinforcement. Several techniques for delivery are satisfactory, but most investigators would suggest discharging the inhaler when it is 1 to 1½ inches (2 fingers) away from the open mouth. The patient should then take a slow, deep inspiration, from functional residual capacity to total lung capacity, and then hold the breath for 8 to 10 seconds. This technique improves deposition and can result in nearly doubling the amount of medication that reaches the lower respiratory tract. In patients with poor technique, delivery can be improved by using a spacer. Typically, 2 to 3 minutes should elapse between the first and second puffs from an aerosol bronchodilator so that the maximal bronchodilating effect of the first puff can permit better penetration of the second puff.<sup>42</sup>

With environmental concerns about ozone depletion as a result of the extensive industrial use of chlorofluorocarbons (CFCs), the development of nonCFC and powder formulations of selected beta<sub>2</sub>-agonist preparations has resulted in a nonCFC formulation. These may also be advantageous for

patients who are prone to the irritant effects of a freon-metered device.

Oral beta-agonist preparations are available, but inhalation delivers more of the active drug directly to the mucosal surface and, at the same time, minimizes side effects. Oral therapy may be useful in certain situations (eg, acute viral infection) in which airway irritation prevents the comfortable use of an inhaled therapeutic agent. Side effects associated with beta-agonist therapy include tremor, nervousness, and, with higher doses of even the selective beta<sub>2</sub> agents, palpitations or tachycardia.

*Anticholinergic Agents.* The parasympathetic nervous system appears to play a prominent role in cold air-induced asthma, SO<sub>2</sub>-induced asthma, and cough-variant asthma. This may be a reflection of direct neural (parasympathetic) activity, reflex cholinergic bronchoconstriction, or the interplay between neural mechanisms and inflammatory mediators.

Ipratropium has been shown to be effective in reducing the cholinergic hyperreactivity that is present in many patients with chronic bronchitis, emphysema, and asthma. It is administered with an MDI (2 puffs every 6 hours as needed). Although the therapeutic response obtained with ipratropium is comparable to albuterol in terms of its bronchodilating effect (ie, an increase in FEV-1), its onset of action is considerably slower (15 to 30 minutes).<sup>42</sup>

### **Immunotherapy**

Numerous studies with pollens (eg, weeds, grasses, trees), animal allergens, and dust mites support the efficacy of immunotherapy in treating allergic rhinitis. However, only a few well-controlled studies that evaluate the role of immunotherapy in treating patients with allergic asthma have been carried out.<sup>76</sup>

Studies that use bronchial provocation with specific allergens (eg, cat, dust mites) have demonstrated the ability to significantly shift the PD<sub>20</sub> FEV-1 (10-fold to 100-fold) in patients who are immunized with an appropriate dose of a standardized extract. Most recently, a major placebo-controlled study of the role of immunotherapy in adults with seasonal ragweed-induced asthma demonstrated improvement in the ragweed-immunized patients both in clinical endpoints (reduction in asthma symptoms, decreased medication usage, increased PEF measurements) and in objective parameters (a reduction in skin test sensitivity, decreased bronchial responsivity to ragweed upon bronchial provocation, a rise in specific IgG ragweed antibodies, and a blunting of the usual seasonal rise in IgE ragweed antibodies). As in ragweed-induced allergic rhinitis, this study again demonstrates that clinical success hinges on the use of an optimal therapeutic dose of the relevant allergen.<sup>77</sup>

... REFERENCES ...

1. National Institutes of Health National Asthma Education Program Expert Panel Report. Executive summary: Guidelines for the diagnosis and management of asthma Bethesda, MD: US Department of Health and Human Services, June 1991. NIH publication # 91-3042A.
2. National Institutes of Health. Global Initiative for Asthma. Global strategy for asthma management and prevention NHLBI/WHO workshop report (NIH publication #95-3659). Bethesda, MD: US Department of Health and Human Services, Jan 1995.
3. Creticos PS. Immunologic changes associated with immunotherapy: Immunotherapy of IgE-mediated disorders. In: Greenberger PA, ed. *Immunology and Allergy Clinics of North America* Philadelphia, PA: WB Saunders Company;1992;12:13-37.
4. Cousins DJ, Staynov DZ, Lee TH. Regulation of IL-4, IL-5 and GM-CSF in T lymphocytes. In: Marone G, Austen KF, Holgate ST, Kay AB, Lichtenstein LM, eds.

*Asthma and Allergic Diseases: Physiology, Immunopharmacology and Treatment* San Diego, CA: Academic Press; 1998:193-203.

5. Kay AB. T lymphocytes in chronic asthma. In: Marone G, Austen KF, Holgate ST, Kay AB, Lichtenstein LM, eds. *Asthma and Allergic Diseases: Physiology, Immunopharmacology and Treatment* San Diego, CA: Academic Press; 1998:207-221.
6. Varney VA, Hamid QA, Gaga M, et al. Influence of grass pollen immunotherapy on cellular infiltration and cytokine mRNA expression during allergen-induced late-phase cutaneous responses. *J Clin Invest* 1993;92:644-651.
7. Naclerio RM, Meier HL, Kagey-Sobotka A, et al. Mediator release after nasal challenge with allergen. *Am Rev Respir Dis* 1983; 128:597-602.
8. Creticos PS, Peters SP, Atkinson NF Jr, et al. Peptide leukotriene release after antigen challenge in patients sensitive to ragweed. *N Engl J Med* 1984;310:1626-1630.
9. Naclerio RM, Proud D, Togias AG, et al. Inflammatory mediators in late antigen-induced rhinitis. *N Engl J Med* 1985;313: 65-70.
10. Casale TB, Wood D, Richerson HB, et al. Direct evidence of a role for mast cells in the pathogenesis of antigen-induced bronchoconstriction. *J Clin Invest* 1987;80: 1507.
11. Liu MC, Hubbard WC, Proud D, et al. Immediate and late inflammatory responses to ragweed antigen challenge of the peripheral airways in allergic asthmatics. *Am Rev Respir Dis* 1991;144:51.
12. Creticos PS. Patient education in the United States. Proceedings of the XV International Congress of Allergology and Clinical Immunology and the 1994 Annual Meeting of the European Academy of Allergology and Clinical Immunology, Stockholm, June 26-July 1, 1994. *Progress in Allergy and Clinical Immunology*. S.G.O. Johansson, ed. Stockholm: Hogrefe & Huber Publishers; 1995;3:156-159.
13. Agarwal MK, Swanson MC, Reed CE, Yunginger JW. Immunochemical quantitation of airborne short ragweed, Alternaria, antigen E, and Alt-1 allergens: A two-year prospective study. *J Allergy Clin Immunol* 1983;74:40-45.
14. Barnes PJ. Inhaled glucocorticoids for asthma. *N Engl J Med* 1995;332:868-875.
15. Barnes PJ. Antiinflammatory actions of glucocorticoids: Molecular mechanisms. *Clin Sci* 1998;94:557-572.

16. Laitinen A, Haahtela T. A comparative study of the effects of an inhaled corticosteroid, budesonide, and a beta<sub>2</sub>-agonist, terbutaline, on airway inflammation in newly diagnosed asthma: A randomized, double-blind, parallel-group controlled trial. *J Allergy Clin Immunol* 1992;83:554-562.
17. Haahtela T, Jarvinen M, Kava T, et al. Comparison of a beta<sub>2</sub>-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325:388-392.
18. Woolcock A, Lundback B, Ringdal N, Jacquest LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose if inhaled steroids. *Am J Resp Crit Care Med* 1996;153:1481-1488.
19. Selroos O, Pietinalho A, Löfroos A, Riska H. Effect of early vs late intervention with inhaled corticosteroids in asthma. *Chest* 1995;108:1228-1234.
20. Schleimer RP. Effects of glucocorticoids on inflammatory cells relevant to their therapeutic applications in asthma. *Am Rev Respir Dis* 1990;141:S59-S69.
21. Barnes PJ, Adcock I. Anti-inflammatory actions of steroids: Molecular mechanisms. *TIPS* 1993; 14:436-441. [Review of mechanisms of action of corticosteroids.]
22. Dahlberg E, Thalén A, Brattsand R, et al. Correlation between chemical structure, receptor binding, and biological activity of some novel, highly active, 16 cx, 17 cx acetal-substituted glucocorticoids. *Mol Pharmacol* 1984;25:70-78.
23. Johnson M. Pharmacodynamics and pharmacokinetics of inhaled glucocorticoids. *J Allergy Clin Immunol* 1996;97: 169-176.
24. Kelly WH. Pharmacokinetic/pharmacodynamic comparison of the inhaled corticosteroids. *J Allergy Clin Immunol* 1998;102: S36-S51.
25. National Heart, Lung, and Blood Institute. Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Institutes of Health; 1997. Publication 97-4051.
26. Sorkness CA. Establishing a therapeutic index for the inhaled corticosteroids: Part II. *J Allergy Clin Immunol* 1998;102:S52-S64.
27. Toogood JH. Side effects of inhaled corticosteroids. *J Allergy Clin Immunol* 1998;102:705-712.
28. Kamada KA, Szeffler SJ, Martin RJ, et al. Issues in the use of inhaled glucocorticoids. *Am J Resp Crit Care Med* 1996;153: 1739-1748.
29. Allen DB, Bronsky EA, LaForce CF, et al. Growth in asthmatic children treated with fluticasone propionate. *J Pediatrics* 1998;132:472-477.
30. Shapiro G, Konig P. Cromolyn sodium: A review. *Pharmacotherapy* 1985;5:156-170.
31. Blumenthal MN, Selcow J, Spector S, Zeiger RS, Mellon M. A multicenter evaluation of the clinical benefits of cromolyn sodium aerosol by metered-dose inhaler in the treatment of asthma. *J Allergy Clin Immunol* 1988;81:681-687.
32. Petty TL, Rollins DR, Christopher K, Good JT, Oakley R. Cromolyn sodium is effective in adult chronic asthmatics. *Am Rev Respir Dis* 1989;139:694-701.
33. Creticos PS. Effects of nedocromil sodium on inflammation and symptoms in therapeutic studies. *J Allergy Clin Immunol* 1996;98(suppl):S143-S150.
34. Bel EH, Timmers MC, Hermans J, Dijkman JH, Sterk PJ. The long-term effects of nedocromil sodium and beclomethasone depropionate on bronchial responsiveness to methacholine in nonatopic asthma subjects. *Am Rev Respir Dis* 1990;141:21-28.
35. Rebusck AS, Kesten S, Boulet LP, et al. A 3-month evaluation of the efficacy of nedocromil sodium in asthma: A randomized, double-blind, placebo-controlled trial of nedocromil sodium conducted by a Canadian multicenter study group. *J Allergy Clin Immunol* 1990;85:612-617.
36. North American Tilade Study Group. A double-blind multicenter group comparative study of the efficacy and safety of nedocromil sodium in the management of asthma. *Chest* 1990;97:1299-1306.
37. Creticos PS, Burk J, Smith L, Comp R, Norman PS, Findlay S. The use of twice daily nedocromil sodium in the treatment of asthma. *J Allergy Clin Immunol* 1995;95: 829-836.
38. Szeffler SJ, Nelson HS. Alternative agents for anti-inflammatory treatment of asthma. *J Allergy Clin Immunol* 1998;102(suppl): S23-S35.
39. Lal S, Dorow PD, Venho KK, Chatterjee SS. Nedocromil sodium is more effective than cromolyn sodium for the treatment of chronic reversible obstructive airway disease. *Chest* 1993;104:438-447.
40. Kraft M, Wenzel SE, Bettinger CM, Martin RJ. The effect of salmeterol on nocturnal symptoms, airway function and inflammation in asthma. *Chest* 1997;111:1249-1254.
41. Pearlman DS, Chervinsky P, LaForce L, et al. A comparison of salmeterol with albuterol in the treatment of mild-to-moder-

- ate asthma. *N Engl J Med* 1992;327:1420-1425.
42. Creticos PS. Asthma in Adults. In: Jerome P. Kassirer, Harry L. Greene II, eds. *Current Therapy in Adult Medicine* Mosby Year-Book, Inc. 4th ed. 1997:757-765.
43. Henderson WR. The role of leukotrienes in inflammation. *Ann Intern Med* 1994;121:684-697.
44. Holgate ST, Bradding P, Sampson AP. Leukotriene antagonists and synthesis inhibitors: New directions in asthma therapy. Review. *J Allergy Clin Immunol* 1998;98:1-13.
45. Liu MC, Dubé LM, Lancaster J. The Zileuton Study Group. Acute and chronic effects of a 5-lipoxygenase inhibitor in asthma: A 6-month randomized multicenter trial. *J Allergy Clin Immunol* 1996;98:859-871.
46. Fish JE, Kemp JP, Lockey RF, et al. Zafirlukast for symptomatic mild-to-moderate asthma: A 13-week multicenter study. *Clin Ther* 1997;19:675-690.
47. Reiss TF, Chervinsky P, Dockhorn RJ, et al. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma. *Arch Intern Med* 1998;158:1213-1220.
48. Laviolette M, Malmstrom K, Lu S, et al. Montelukast added to inhaled beclomethasone in treatment of asthma. *Am J Respir Crit Care Med* 1999;160:1862-1868.
49. Busse W, Nelson H, Wolfe J, et al. Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. *J Allergy Clin Immunol* 1999;103:1075-1080.
50. Fish J, Boone R, Emmett A, et al. Salmeterol added to inhaled corticosteroids provides greater asthma control compared to monelukast. *Am J Respir Crit Care Med* 2000;161:A203 [abstract].
51. Kelly HW, Davis RL. Asthma. In: DiPiro JT, Talbert RL, Hayes PE, Yee GC, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach* New York, NY: Elsevier Science Publishing Co., Inc;1989:347-367.
52. Chung KF, Patel HJ, Fadlon EJ, et al. Induction of eotaxin expression and release from human airway smooth muscle cells by IL-1 $\beta$  and TNF $\alpha$ : Effects of IL-10 and corticosteroids. *Brit J Pharm* 1999;127:1145-1150.
53. Elias JA, Wu Y Zheng T, Panettieri R. Cytokine- and virus- stimulated airway smooth muscle cells produce IL-11 and other IL-6-type cytokines. *Am J Physiol* 1997;273:L648-L655.
54. Creticos PS. Drug therapy of asthma. Smith & Reynard: *Textbook of Pharmacology* W.B. Saunders Company Publishers; 1992:1051-1066.
55. Product information for SEREVENT (salmeterol xinafoate) DISKUS September 1998. RL-628. Glaxo Wellcome Inc, Research Triangle Park, NC.
56. Dowling RB, Johnson M, Cole PJ, Wilson R. Effect of fluticasone propionate and salmeterol on *Pseudomonas aeruginosa* infection of respiratory mucosa in vitro. *Eur Respir J* 1999;14:363-369.
57. Hasani A, Toms N, O'Connor J, et al. The effect of salmeterol xinafoate on lung mucociliary clearance in patients with stable asthma. *Eur Respir J* 1998;12(suppl):180.
58. Devalia JL, Sapsford RJ, Rusznak C, et al. The effects of salmeterol and salbutamol on ciliary beat frequency of cultured human bronchial epithelial cells, in vitro. *Pulm Pharmacol* 1992;5:257-263.
59. Eickelberg O, Roth M, Lörx R, et al. Ligand-independent activation of the glucocorticoid receptor by beta<sub>2</sub>-adrenergic receptor agonists in primary human lung fibroblasts and vascular smooth muscle cells. *J Biol Chem* 1999;274:1005-1010.
60. Oddera S, Silvestri M, Testi R, Rossi GA. Salmeterol enhances the inhibitory activity of dexamethasone on allergen-induced blood mononuclear cell activation. *Respiration* 1998;65:199-204.
61. Anenden V, Engemba G, Kessel B, Johnson M, Costello J, Kilfeather S. Salmeterol facilitation of fluticasone-induced apoptosis in eosinophils of asthmatics pre- and post-antigen challenge. *Eur Respir J* 1998;12:157S.
62. Baraniuk JN, Ali M, Brody D, et al. Glucocorticoids induce beta<sub>2</sub>-adrenergic receptor function in human nasal mucosa. *Am J Respir Crit Care Med* 1997;155:704-710.
63. Sue-Chu M, Wallin A, Wilson S, et al. Bronchial biopsy study in asthmatics treated with low-and high-dose fluticasone propionate (FP) compared to low-dose FP combined with salmeterol. *Eur Respir J* 1999;30:124.
64. Greening AP, Ind PW, Northfield M, et al. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994;344:219-224.
65. Kelsen SG, Church NL, Gillman SA, et al. Salmeterol added to inhaled corticosteroid therapy is superior to doubling the dose of inhaled corticosteroids: A randomized clinical trial. *J Asthma* 1999;36:703-715.
66. Murray JJ, Church NL, Anderson WH, et

- al. Concurrent use of salmeterol with inhaled corticosteroids is more effective than inhaled corticosteroid dose increases. *Allergy and Asthma Proc* 1999;20:173-180.
- 67.** Condemi JJ, Goldstein S, Kahlberg C, et al. The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. *Ann Allergy Asthma Immunol* 1999;82:383-389.
- 68.** Baraniuk J, Murray JJ, Nathan RA, et al. Fluticasone alone or in combination with salmeterol vs triamcinolone in asthma. *Chest* 1999;116:625-632.
- 69.** Pearlman DS, Stricker W, Weinstein S, et al. Inhaled salmeterol and fluticasone propionate: A study comparing monotherapy and combination therapy in asthma. *Ann Allergy Asthma Immunol* 1999;82:257-265.
- 70.** Van Noord JA, Schreurs AJM, Mol SJM, Mulder PGH. Addition of salmeterol versus doubling the dose of fluticasone propionate in patients with mild to moderate asthma. *Thorax* 1999;54:207-212.
- 71.** Kavuru M, Melamed J, Gross G, et al. Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma: A randomized, double-blind, placebo controlled trial. *J Allergy Clin Immunol* 2000;104:1108-1116.
- 72.** Shapiro G, Lumry W, Wolfe J, et al. Combined salmeterol 50 mcg and fluticasone propionate 250 mcg in the DISKUS device for the treatment of asthma. *Am J Respir Crit Care Med* 2000;161:527-534.
- 73.** Aubier M, Pieters WR, Schollosser JH, et al. Salmeterol/fluticasone propionate (50/500 mcg in combination in a DISKUS inhaler (Seretide) is effective and safe in the treatment of steroid dependent asthma. *Respir Med* 1999;93:876-884.
- 74.** Tattersfield AE, Postma DS, Barnes PJ, et al. Exacerbations of asthma. *Am J Respir Crit Care Med* 1999;160:594-599.
- 75.** Matz J, Kalberg C, Emmett A, Yancey S, Dorinsky P, Rickard K. The combination of salmeterol and low-dose fluticasone versus higher-dose fluticasone: An analysis of asthma exacerbations. *J Allergy Clin Immunol* 2000;105:S21 [abstract].
- 76.** Creticos PS. The consideration of immunotherapy in the treatment of allergic asthma. *J Allergy Clin Immunol* 2000;105:S559-S574.
- 77.** Creticos PS, Reed CE, Norman PS. Ragweed immunotherapy in adult asthma. *N Engl J Med* 1996;334:501-506.