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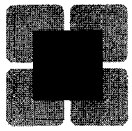

Asthma: current controversies and emerging therapies

MANI S. KAVURU, MD; LILY PIEN, MD; DIANNE LITWIN, MD; SERPIL ERZURUM, MD; MUZAFFAR AHMAD, MD

SUMMARY Despite advances in understanding the pathogenesis of asthma, a number of controversies regarding the optimal clinical management of asthma remain. This review of recent literature and current controversies, chosen mainly on the basis of relevance to clinical therapy, is directed toward nonspecialists caring for asthmatic patients.

KEY POINTS Recent evidence indicates asthma is mediated by airway inflammation, and maintenance therapy should include inhaled anti-inflammatory drugs. Inhaled corticosteroids are usually the first choice. However, adverse effects of long-term use are just being recognized. Optimal dosage, spacer devices, and gargling reduce these effects. Although inhaled beta agonists are essential for acute asthma management, their use in regular maintenance therapy is under reevaluation. Excessive use of beta agonists usually indicates the need for more effective anti-inflammatory therapy.

All patients should avoid allergens. A subset of asthma patients who fail to respond to treatment may benefit from immunotherapy, but there are risks. Emergency management of acute asthma should include early and frequent administration of aerosolized beta agonists and almost universal therapy with corticosteroids.

INDEX TERMS: ASTHMA; ADRENERGIC BETA RECEPTOR AGONISTS; INFLAMMATION; ANTI-INFLAMMATORY AGENTS; IMMUNOTHERAPY
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From the Department of Pulmonary and Critical Care Medicine, The Cleveland Clinic Foundation.

Address reprint requests to M.S.K., Department of Pulmonary and Critical Care Medicine, A90, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

AN EXPLOSION of recent information has implicated airway inflammation in the pathogenesis of airway hyperreactivity and asthma.[1] However, even though our understanding of the pathogenesis of asthma has increased in the past decade, so has asthma morbidity and mortality.[2,3] There are several possible reasons for these trends, but no general agreement.

In light of these trends, a number of controversies exist as to the optimal clinical management of asthma: (1) For maintenance therapy of chronic asthma, what are the optimal inhaled anti-inflammatory agents (corticosteroids, cromolyn, or nedocromil)? (2) What is the role of inhaled beta agonists in the increased mortality rate? (3) What is the role of inflammation in sudden vs gradual decompensation? (4) In status asthmaticus, what are the roles of nebulized beta agonists given continuously and intravenous aminophylline? (5) What is the role of immunotherapy? (6) What is the status of emerging, experimental therapies? This paper will explore each of these controversies point by point.

MAINTENANCE THERAPY FOR CHRONIC ASTHMA

Historically, asthma was viewed as a reversible bronchospastic disorder marked by smooth-muscle contraction. However, patients who die of status asthmaticus have extensive inflammatory changes of the airways, including mucous plugging, extensive epithelial sloughing, and inflammatory cellular infiltration of the mucosa and submucosa.[4] Studies of experimentally induced asthma and studies involving bronchoalveolar lavage and endobronchial biopsy in patients with mild, chronic asthma have contributed to the hypothesis that airway inflammation is a fundamental aspect of asthma.[5–7] This concept underlies the growing clinical and investigational interest in the use of anti-inflammatory agents such as inhaled steroids, cromolyn, and nedocromil in treating asthma.

Inhaled steroids

A number of recent bronchoalveolar lavage and biopsy studies have shown that 3 months' therapy with inhaled corticosteroids reduces inflammatory changes in patients with bronchial asthma.[8–10] Interestingly, a study by Lungren[11] showed that basement-membrane thickening persists even after 10 years of such therapy. Additional studies have shown that inhaled steroids reduce airway responsiveness to methacholine, histamine, or exercise. This reduction in responsiveness (as assessed by an increase in provocative concentration of histamine or methacholine) occurs over several weeks to several months, and usually ranges in the order of one or two doubling dilutions.[12,13] Some have questioned whether these slight changes have clinical significance.[14]

Recent data. Numerous recent studies have shown that inhaled steroids effectively control the symptoms of chronic asthma. Haahtela[15] conducted a prospective parallel-group trial lasting 2 years, in which 103 patients were randomly assigned to receive 600 µg of inhaled budesonide twice a day or 375 µg of inhaled terbutaline twice a day. Asthma had been diagnosed in the previous 1 year and for the most part was mild. The budesonide group enjoyed a significant reduction in symptoms, needed "rescue" with beta agonists less, and experienced an improvement in morning and evening peak expiratory flow rates. This study is limited in that the beta agonist was only given twice a day and that a spacer device was not specified for either group. Kertjens et al[16] noted that inhaled beclomethasone at 800 µg per day improved symptoms and lung function over a 2.5-year period in patients with chronic asthma when given in addition to beta-agonist inhaled therapy. A number of studies have shown that higher doses of inhaled steroids reduce the need for maintenance oral steroids.[17–19]

Recognition of side effects. The side effects of inhaled corticosteroids are being increasingly recognized as a potential problem. Toxicity varies with the total dose, the dosing schedule, use of a spacer device, mouth rinsing, and the sensitivity of the parameter used to assess systemic toxicity.[13,20] The adverse effects of inhaled corticosteroids can be broadly classified as topical or systemic. The three main topical side effects are cough, oral candidiasis, and dysphonia. Slow inhalation, use of a spacer device, and gargling reduce the incidence of these side effects.[21] The systemic side effects may include suppression of the hypothalamic-pituitary-adrenal (HPA) axis, adverse effects on bone metabolism (leading to osteoporosis), slowing of growth in children and adolescents, cataracts, bruising, dermal thinning, and psychological changes. Many studies have suggested that doses of inhaled corticosteroids in excess of 800 µg/day in adults or 400 µg/day in children can suppress the HPA axis in a dose-related manner, although the response varies substantially among individuals.[20] HPA-axis suppression has been most commonly assessed by measuring the morning serum cortisol level and 24-hour urinary cortisol excretion. The clinical significance of these changes over the long duration is not known. In patients who require more than 800 µg, the use of a spacer device in conjunction with a metered-dose inhaler (MDI) and the use of mouthwashing may reduce suppression of the HPA axis. Twice-a-day dosing appears to have fewer side effects. Some studies suggest that, at higher doses, beclomethasone may have a somewhat greater propensity to produce adrenal suppression than budesonide does, although the relevance of this is not clear. Inhaled corticosteroids in doses as low as 400 µg/day have been associated with the development of osteoporosis.[22]

Cromolyn sodium

A large number of studies have documented the protective effect exerted by cromolyn sodium (CS) against provocative stimuli such as allergens, cold air, SO_2, and exercise.[23] The drug is most effective

when administered before challenge. The protective effects against nonspecific agents such as methacholine and histamine have been less established.[24] A number of studies have evaluated the effect of CS on nonspecific bronchial hyperreactivity. Studies in which CS was administered for longer than 6 weeks suggest airway reactivity decreases.

Despite initial notions that CS would be more effective in extrinsic than intrinsic asthma, most carefully designed studies do not support this concept.[23] About 60% to 79% of asthma patients show a response to CS.[23] A 3-month, double-blind, placebo-controlled clinical trial found CS effective in chronic adult asthma.[25] Studies comparing CS and theophylline in the short-term management of chronic asthma suggest that both of these agents are equally effective, with perhaps greater side effects with theophylline.[26] There are some data to show that there is an additive effect between these two agents.[23] A study by Shapiro et al[27] demonstrated that CS was as effective as triamcinolone in children. However, in a 6-month trial in adult patients, CS did not reduce the need for beclomethasone.[28]

Nedocromil sodium

Nedocromil sodium (NS) was approved in the United States in 1993 for use in MDIs. NS is structurally different from CS but has very similar pharmacologic activities and a similar mechanism of action. A number of in vitro and in vivo studies suggest that NS blocks both the early and late asthmatic response, has anti-inflammatory effects on a number of cells, and may be more potent than CS is in inhibiting bronchial C-fiber nerve endings.

A recent meta-analysis reviewed all known placebo-controlled, double-blind, randomized clinical trials of NS (a total of 4723 patients from 127 centers).[29] This included both published and unpublished material. The authors compared the effects of NS and placebo using six efficacy variables, including symptom scores, peak flows, forced expiratory volume in 1 second (FEV_1), and inhaled bronchodilator use. The study found NS more effective than placebo and of most benefit to patients receiving monotherapy with bronchodilators.[30–32] The aggregate data suggested that NS is less potent than inhaled corticosteroids, although some inhaled corticosteroid-sparing effects were noted. A recent NS workshop concluded that NS could represent an alternative to CS, although it has no clear advantage over inhaled steroids and costs more.[33]

Chronic asthma: recommendations

Overall, inhaled anti-inflammatory agents should be part of the maintenance regimen for most patients with chronic asthma. Inhaled corticosteroids are preferred in most patients because of proven efficacy, greater potency than CS or NS, and effectiveness when administered twice a day as opposed to four times a day.[34] Also, there are more data supporting improvement of inflammation as assessed by bronchoalveolar lavage and endobronchial biopsy in patients treated with inhaled corticosteroids.[35] In patients at risk of toxicity from inhaled corticosteroids (ie, children or patients requiring high doses of inhaled corticosteroids), CS or NS are rational alternatives. Also, in patients who continue to have symptoms despite very high doses of inhaled corticosteroids, the addition of NS seems reasonable.[35–37] Additional studies directly comparing inhaled corticosteroids and NS for newly diagnosed bronchial asthma are required.

DO BETA AGONISTS INCREASE MORTALITY?

Much controversy surrounds the possible role of beta agonists in the increasing asthma mortality rate.[14,38,39] According to one hypothesis, excessive or regular use of beta-adrenergic bronchodilators can actually worsen asthma, perhaps contributing to morbidity and mortality. Several studies from New Zealand suggested that inhaled beta agonists increase the risk of death in severe asthma.[40,41]

In patients with mild, stable asthma, Sears et al[42] evaluated the effects of regular vs "on-demand" inhaled fenoterol therapy in a 24-week, placebo-controlled, crossover study. In the 57 patients who did better with one of the two regimens, only 30% had better asthma control when taking fenoterol on a regular schedule, whereas 70% did better when they used it only as needed. This study has been widely criticized,[39] for several reasons: (1) The patients had mild asthma, requiring only 2.9 doses per day via an MDI, and were excluded if they required more than eight doses per day. (2) The beta agonist employed, fenoterol, produces significantly greater beta-adrenergic stimulation and has an intrinsically shorter duration of action than beta agonists used in the United States. (3) Subjects were not permitted to use any other bronchodilators. (4) The data

presented in the study were qualitative, with no indication of the magnitude of the differences or means of assessing possible clinical significance.

In a second well-publicized, matched, case-control study, Spitzer et al[43] used a health insurance data base from Saskatchewan, Canada to identify a cohort of 12 301 patients for whom asthma medications had been prescribed. The investigators matched 129 case patients who had fatal or near-fatal asthma with 655 controls. The use of a beta agonist via an MDI was associated with an increased risk of death from asthma, an odds ratio of 5.4 per canister of fenoterol and 2.4 per canister of albuterol.

The primary limitation of this study, and indeed, case-control studies in general, is that the two groups may have differed in the severity of the underlying disease. Because sicker patients were both more likely to die and more likely to have received an inhaled beta agonist, it is difficult to judge the independent effect of the drug. Indeed, the subjects who died used all antiasthma medications more than the controls did. However, in a subsequent report, the same authors adjusted for disease severity and still found a significant correlation between beta-agonist use and asthma mortality.[44]

A recent meta-analysis evaluated the association between beta-agonist use and death due to asthma in six case-control studies. Statistical integration revealed a significant, although extremely weak, relation between beta-agonist use and asthma death, but only for beta agonists given with a nebulizer, not with an MDI.[45]

Beta agonist use: recommendations

Overall, the exact contribution of beta agonists to the recent mortality trend remains unknown. There is sufficient concern regarding fenoterol to justify avoiding its use. Also, if patients require an increasing number of puffs of other beta-agonist aerosols, this usually indicates the need for more effective anti-inflammatory therapy. Beta-agonist aerosols remain a critical part of the regimen for acute emergency management of bronchial asthma. However, whether they should be avoided in long-term maintenance therapy remains unknown. The National Asthma Education Program (NAEP) guidelines recommend that inhaled beta agonists be used as needed.[1] If a patient needs more than three or four puffs a day of a beta agonist, additional therapy should be considered.

WHAT IS THE ROLE OF INFLAMMATION IN SUDDEN VS GRADUAL DECOMPENSATION?

Although inflammation is now understood to play a fundamental role in asthma, the relationship between airway inflammation and bronchial hyperreactivity remains unclear.[46,47] Also, whether inflammation is as important in the subset of patients who present with sudden, "hyperacute" decompensation remains poorly understood.

Numerous retrospective studies have examined the circumstances of asthma-related deaths.[48–50] In addition, several case-control studies compared patients who died of asthma with matched survivors.[51,52] These and other studies suggest that asthma deaths can be classified as either type 1 (slow-onset, late-arrival) or type 2 (sudden-onset).[53] The consensus from these studies is that several risk factors contribute to type-1 fatal asthma, including previous serious asthma requiring emergency-room visits or mechanical ventilation. Socioeconomic status, psychological features, race, and culture may interfere with compliance and access to medical care. Other factors include failure to perform pulmonary function testing to objectively assess asthma severity. Inadequate treatment with either inhaled or systemic anti-inflammatory agents is also frequently described. Therefore, underestimation of asthma severity and undertreatment of asthma are important contributing factors in type-1 asthma-related fatalities.[54]

A number of recent studies have highlighted that some patients die suddenly and unexpectedly of acute (type 2) asthma. Wasserfallen[55] analyzed the interval between onset of symptoms and endotracheal intubation in 34 patients who required intubation and mechanical ventilation because of severe asthma. Three patterns of decompensation were noted: rapid (less than 3 hours), gradual (9.2 ± 7.7 days), and acute after unstable asthma (4.2 ± 3.6 days). The rapid, sudden, asphyxic type was more frequent in young men and was associated with extreme hypercapnia and a higher incidence of respiratory arrest, but these patients recovered faster and did not need mechanical ventilation as long. The authors suggested that bronchospasm was a primary mechanism in this group.

Kallenbach[56] studied 81 patients who had acute asthma that required mechanical ventilation. Patients with hyperacute attacks in which less than 3 hours elapsed from onset of attack to mechanical

ventilation had a significantly higher rate of near-fatality. They also had a more rapid response to bronchodilators and a shorter duration of mechanical ventilation. Sur et al[57] studied the histologic differences in the airways of three patients who died of sudden-onset (type 2) asthma and four patients who died of the more common, slow-onset (type 1) asthma. In the sudden-onset group, neutrophils exceeded eosinophils in the airway submucosa. The authors concluded that sudden-onset fatal asthma is immunohistologically distinct from slow-onset fatal asthma.

Status asthmaticus: recommendations

Therefore, a relatively small subset of patients appears to have status asthmaticus that has a predominately hyperacute, bronchospastic component.[58,59] Whether the fundamental mechanism in this subset is bronchospasm or a yet-unknown inflammatory process remains to be established. Certainly, any patient with status asthmaticus should be maximally treated with an inhaled beta agonist and a systemic anti-inflammatory drug.[60]

EMERGENCY MANAGEMENT

For patients who have acute, severe asthma, there is debate about the best way to administer beta agonists and whether the use of aminophylline is appropriate.

Nebulized beta agonists: continuous or intermittent?

Even though in many studies beta agonists produced comparable bronchodilation whether given via an MDI or a nebulizer,[61–63] the NAEP expert panel recommends wet nebulization for emergency management of asthma.[1] Nebulized therapy continues to be widely used, for a number of reasons. Acutely tachypneic patients are felt not to be able to optimally use MDIs, even with a "spacer" device. Further, patients usually use an MDI at home, and an acute episode requiring emergency care typically represents a failure of home therapy for which patients expect a different form of therapy. Finally, there is a continued, widespread belief that nebulized therapy is more effective than MDI therapy in treating acute exacerbation of airway obstruction.

Much evidence suggests that patients with acute, severe airflow obstruction need higher dosages of aerosolized beta agonists than do those with less severe, stable airway obstruction. In many hospitals, standard therapy for acutely ill patients involves giving a beta agonist at 20- to 30-minute intervals. A number of studies have suggested that beta agonists may be effective and safe when given continuously by a variety of nebulization devices for up to 72 or 96 hours in children.[64,65] Two studies have extended these findings to adults.[66,67]

Colacone and associates[66] randomly assigned 42 patients with acute, severe asthma to receive either 5 mg of albuterol by intermittent bolus nebulization immediately and 60 minutes later or 0.2 mg/mL continuously by a calibrated nebulizer with an output of 25 mL/hour. Each patient received 10 mg of albuterol over 2 hours. The authors found both regimens equally effective and well tolerated. Interestingly, the heart rate was significantly higher at 30 and 90 minutes in the bolus nebulization group than in the continuous nebulization group.

Olshaker and associates[67] performed an open-label, prospective study in 76 adults who had acute asthma exacerbations. The patients were given three continuous nebulizer treatments over 45 minutes in the emergency room; each dose contained 2.5 mg of albuterol and 3 mL of normal saline. All patients showed objective and subjective improvement, including an average improvement in peak flow of 150% over baseline. This therapy was well tolerated and produced no significant tachyrhythmia, even though the patients had underlying hypertension and coronary artery disease.

In a study by Lin and colleagues,[68] seven adults (mean age 30.9 years) with asthma were given nebulized albuterol at 0.4 mg/kg/hour continuously for 4 hours. Patients with coronary artery disease were excluded. The FEV_1 improved significantly, and the mean heart rate increased by 16.3%. One patient withdrew because of supraventricular tachycardia. Six of the seven patients had serum albuterol levels greater than 25 ng/mL at the end of treatment. The authors concluded that continuous use of high-dose, nebulized albuterol can result in markedly high serum albuterol levels and potential cardiac stimulation in some patients.

Patients with acute airflow obstruction refractory to intermittent, frequent, aerosolized beta-agonist therapy may be candidates for continuous therapy with a nebulized bronchodilator while awaiting the effects of anti-inflammatory therapy.[69] Recommended regimens are albuterol 2.5 to 15 mg/hour or terbutaline 2 to 8 mg/hour. A variety of delivery

methods for continuous nebulization have been described. Patients should receive continuous treatment until they have improved enough to tolerate intermittent aerosol treatment every 4 hours. Extensive experience in children and the two reports in adults suggest that this approach is safe, although further studies in adults with underlying coronary artery disease are required.

Aminophylline

The role of aminophylline in the treatment of acute, severe asthma remains controversial. The NAEP expert panel on the diagnosis and management of asthma did not recommended using aminophylline routinely in the emergency treatment of asthma. However, both the NAEP expert panel and the British Thoracic Society did recommend the routine use of oral or intravenous theophylline in patients admitted to the hospital for an acute exacerbation of asthma.[1,70] Early studies in the emergency room suggested that the addition of aminophylline to maximal therapy with inhaled beta agonists had little effect on pulmonary function during 3 hours of observation.[71–73] A recent meta-analysis of 13 controlled trials found no overall benefit of using aminophylline: three studies favored aminophylline therapy, three favored a control regimen consisting of albuterol, epinephrine, or other sympathomimetic bronchodilators, and seven showed no difference between the two.[74]

More recently, a number of studies have evaluated the role of aminophylline in the treatment of acute exacerbation of asthma when used in addition to inhaled beta agonists and intravenous corticosteroids both in the emergency room and in the hospital for both adults and children.[75–80] In a prospective study of 133 adult patients maximally treated with intravenous corticosteroids and inhaled beta agonists, patients who received aminophylline had a threefold lower hospital admission rate (6%) than did placebo recipients (21%).[76] This was surprising, because aminophylline produced no effect on pulmonary function as measured by spirometry. The admission decision was made by house staff not involved in the study, who used preexisting guidelines for admission.

Huang,[78] in a placebo-controlled randomized trial of aminophylline infusion in addition to inhaled albuterol and intravenous methylprednisolone, found the improvement in FEV_1 at 3 hours was greater in the aminophylline group (29% ± 23% compared with 10% ± 10%) and that the aminophylline-treated patients required fewer doses of nebulized albuterol. A concern with this study is whether the patients received maximal dosages of the inhaled beta agonist. Also, it is unclear how the decision to administer "as-needed" albuterol therapy was made, even though this was one of the end points of the study. In contrast, two recent studies in children maximally treated with nebulized albuterol and intravenous corticosteroids did not find the addition of intravenous aminophylline beneficial.[79,80]

Emergency management: recommendations

In summary, emergency management of acute asthma should include early and frequent administration of aerosolized beta agonists and almost universal therapy with systemic corticosteroids. Frequent reassessment for response with a peak flow meter should be performed. Which subset of patients may benefit from continuous aerosolized beta agonists remains poorly understood. Finally, according to NAEP guidelines, aminophylline should be administered only to patients with acute asthma who require hospital admission.[1]

WHAT IS THE ROLE OF IMMUNOTHERAPY IN ASTHMA?

Immunotherapy (IT) has been used to treat allergic disorders since the early 1900s. Although IT has been accepted in the treatment of allergic rhinoconjunctivitis, its use in asthma has been controversial, owing to a number of factors. The pathogenesis of asthma and the role of precipitating triggers, allergic and nonallergic, remain poorly defined. IT is not standardized, having inconsistencies in extract potency and in preparation, methods of administration, and total duration of therapy.

Approximately 100 controlled studies of IT for the treatment of asthma have been performed,[81] some of which were double-blinded. With regard to specific allergens, there is evidence to support the use of dust mite extract,[82,83] pollen extract,[84–86] and cat and dog dander extract.[87,88] Animal dander IT is recommended for patients who cannot avoid animals owing to their occupation, such as veterinarians and laboratory technicians. However, this is not a uniform opinion among allergists. Few studies of mold IT have been done, but efficacy has been demonstrated for *Cladosporium*[89] and *Alternaria*.[90] These studies were performed in Europe, where stand-

ardized mold extract is available. At this time, indications for mold IT are few, as mold extract preparation, purification, and standardization in the United States are unresolved issues.[91] While not all studies of IT have shown benefit, many have shown reduction of asthma symptoms.[82–85,89] Some studies have even indicated decreases in bronchial hyperresponsiveness after long-term IT.[82,86]

Because studies have used different definitions of asthma, different IT regimens, and different outcomes, assessing the efficacy of allergen IT in the treatment of asthma has been difficult. A recent meta-analysis addressing this question included 20 randomized, double-blinded, placebo-controlled trials and demonstrated that allergen IT significantly reduced asthma symptoms, bronchial hyperresponsiveness, and medication requirements in asthmatic patients.[92] The authors concluded that allergen IT is a "useful adjunct to therapy in extrinsic ("allergic") asthma." Further studies to strengthen the role of allergen IT in the treatment of asthma should be multicenter, double-blinded, and placebo-controlled and use standardized allergen extracts. Additional factors, such as nonallergic triggers causing exacerbations and seasonal variation of allergens and of allergic asthma, also need to be addressed in these trials.

Immunotherapy: recommendations

Despite the effectiveness of IT in some studies, recommendations for the treatment of allergic asthma begin with allergen avoidance.[1] This is advised for all asthma patients, regardless of the severity of disease. Second-line treatment is judicious use of asthma medications.[1] With the advent of potent inhaled corticosteroids and effective inhaled beta agonists, many patients can be well controlled with these medications. CS and NS are also effective in allergic asthma.

IT should be considered when: (1) triggers of clinical symptoms clearly correlate with specific allergens; (2) avoidance measures and medications fail to adequately control symptoms; (3) the patient is unable to tolerate asthma medications because of toxicity or adverse effects; (4) allergen exposure is occupationally related and avoidance is unacceptable; (5) seasonal rhinitis occurs concomitantly with seasonal asthma; and (6) the risks and benefits of IT have been thoroughly discussed with the patient. Therefore, IT is not indicated for all asthma patients with positive skin tests, and for many patients, is not even necessary. Moreover, IT can be life-threatening; asthma patients may have more severe reactions to allergy shots than patients receiving IT for allergic rhinitis.[93] The risks must be discussed with the patient and weighed against the benefits.

Therefore, at present, IT in the treatment of allergic asthma is reserved for patients who are unable to achieve substantial relief of symptoms with avoidance measures and pharmacotherapy. It is hoped that future studies with standardized IT will demonstrate more clearly its efficacy. Improved preparations, such as polymerized allergens or allergoids, may also determine the role of IT in asthma therapy, as these may be more effective and safer. While current evidence supports the use of IT in allergic asthma patients, its exact role continues to evolve.

EMERGING THERAPIES

A minority of asthma patients—perhaps 5% to 20%—continue to have troublesome symptoms with frequent exacerbations that necessitate hospitalization despite maximal conventional therapy. The reversible factors that contribute to "steroid-dependent" asthma include noncompliance, poor self-management strategies, inadequate control of allergen burden at home, inadequate inhaler technique, and suboptimal pharmacotherapy. The placebo arms of a number of studies have clearly shown that a compulsive traditional management plan, with frequent follow-up (perhaps in an asthma center), can reduce the need for oral steroids by 16% to 40% in "steroid-dependent" asthma. Numerous studies have demonstrated the efficacy of alternative anti-inflammatory therapies that provide a steroid-sparing effect in asthma. Methotrexate, gold salts, troleandomycin, cyclosporine, leukotriene antagonists, colchicine, chloroquine, gamma globulin, and dapsone are some of the agents that have been investigated.

Glucocorticoid-resistant asthma

Carmichael[94] described 58 patients with chronic asthma in whom the FEV_1 increased less than 15% after a 7-day course of at least 20 mg of prednisolone daily. Dykewicz[95] studied the natural history of asthma in 40 randomly selected adults with asthma refractory to inhaled beclomethasone and beta agonists, and dependent on long-term prednisone therapy (mean duration 6.2 ± 5 years). Over 3 to 5 years, 24 patients (60%) had unchanged prednisone

requirements, 13 patients (32.5%) improved and required less prednisone, and three patients (7.5%) deteriorated and required more prednisone. Unfortunately, this study did not report the maintenance dose of beclomethasone.

Corrigan et al[96] evaluated the possible mechanism of chronic asthma in patients with clinical glucocorticoid resistance (less than a 30% increase in FEV_1 after 2 weeks of daily prednisone treatment, 20 mg for the first week and 40 mg for the second week). Glucocorticoid pharmacokinetics, receptor characteristics, and inhibition of peripheral blood T-cell proliferation by prednisone were assayed. Overall, the investigators noted a relative insensitivity of T lymphocytes to prednisone in patients with clinical glucocorticoid resistance compared with matched glucocorticoid-sensitive patients. They noted that resistance does not reflect abnormal glucocorticoid clearance. Additional studies by this group suggested that activated T lymphocytes may be the target, and perhaps an anti-T-lymphocyte drug such as cyclosporine may be particularly useful in glucocorticoid-resistant asthma.[96] Overall, the clinical relevance of glucocorticoid resistance in patients with chronic steroid-dependent asthma remains speculative and poorly understood.

Methotrexate

Methotrexate, an inhibitor of dihydrofolate reductase, appears to inhibit neutrophil-dependent inflammation. Methotrexate has been evaluated in steroid-dependent asthma in five recent clinical trials,[97–102] following long experience with this drug in rheumatoid arthritis and psoriasis.

Mullarkey et al[97] conducted a placebo-controlled crossover study in 14 steroid-dependent asthma patients. The average starting prednisone dose was 26 mg/day (range 10 to 60 mg). Patients were randomly assigned to receive either placebo or methotrexate (15 mg by mouth per week) for 12 weeks, and then were switched to the alternate form of therapy. They were seen every 3 weeks in follow-up. On the average, patients needed 36.5% less prednisone when they were receiving methotrexate than when they received placebo.

The same group published a follow-up experience of 31 cushingoid asthma patients who were receiving prednisone and inhaled corticosteroids daily. Patients were treated with low-dose methotrexate for 18 to 28 months.[98] The mean prednisone dose declined, from 26.9 mg/day to 6.3 mg/day in the 25 patients who completed the study, and 15 patients stopped using prednisone regularly.

Similarly, Shiner[100] conducted a 24-week, placebo-controlled trial in 69 steroid-dependent asthma patients. The mean daily prednisolone dose was 14.2 mg/day. During 12 weeks of treatment, steroid doses were tapered by 16% in both the methotrexate and placebo groups. However, between 12 and 24 weeks, the prednisolone dose was reduced more in the methotrexate group than in the placebo group (50% vs 14%). Patients were evaluated every 4 weeks in the study. Five of the 38 patients taking methotrexate had liver function abnormalities.

Erzurum et al[101] conducted a double-blind, parallel-group study over 13 weeks in prednisone-dependent asthma (average daily dose 20 mg, range 15 to 30 mg), in which 19 patients received either methotrexate (5 mg intramuscularly every week) or placebo. This study was unique in that patients were seen weekly and there was a 1-month baseline period during which conventional therapy was maximized and attempts to reduce the baseline prednisone dose were made. Overall, both groups reduced their oral prednisone dose by about 40%. The authors concluded that methotrexate did not produce significant benefit in corticosteroid-dependent asthma.

More recently, Coffey et al[102] evaluated 11 subjects who had steroid-dependent asthma (mean prednisone dose 28 mg/day) in a 12-week placebo-controlled crossover trial. The placebo group was able to reduce their prednisone dose by about 20%, and methotrexate was not superior to placebo. In summary, based on the available studies, it is difficult to recommend therapy with methotrexate outside the setting of a clinical trial.

Gold

Both oral and parenteral gold preparations have been used in studies of steroid-dependent asthma.[103–106] In general, the addition of gold decreased corticosteroid requirements, improved symptoms, and perhaps improved bronchial hyperreactivity as well. However, these studies had a number of methodologic limitations. Further, overall patient tolerance was poor: the incidence of side effects, including diarrhea, skin eruptions, and proteinuria, was as high as 37%. There are no data on long-term side effects or patient compliance with gold therapy for patients with bronchial asthma.

Troleandomycin

Another steroid-sparing approach in the treatment of chronic asthma is the use of troleandomycin (TAO), a macrolide antibiotic. A number of open-label studies have demonstrated a reduction in corticosteroid dose when this drug was added to the regimen.[107–110] The principal effect of TAO is the prolongation of plasma half-life of corticosteroids through the inhibition of their elimination; in one study, the methylprednisolone half-life increased from 2.46 hours before TAO therapy to 4.63 hours 1 week after TAO therapy.[108] Published protocols highlight the importance of using methylprednisolone rather than prednisone in conjunction with TAO to have the steroid-sparing effect.[110,111]

A recent, 2-year, placebo-controlled, parallel group study was performed in 75 steroid-dependent asthma patients to compare TAO plus methylprednisolone vs methylprednisolone alone.[112] Patients in both groups achieved alternate-day steroid therapy, and the reduction in methylprednisolone dose was not significantly different between the treatment groups. However, the patients in the TAO group had significantly more steroid-related side effects as assessed by serum levels of IgG, glucose, and cholesterol, and as reflected by osteoporosis. This well-designed study strongly supports the notion that the steroid-sparing properties of TAO are a pharmacologic phenomenon that do not translate into fewer long-term steroid-related side effects. This study indicates that further trials with TAO are probably not indicated.

Cyclosporine

The immunosuppressive agent cyclosporine inhibits mediator release from mast cells and basophils and inhibits the synthesis of lymphokines, with the subsequent down-regulation of $CD4^+$ T lymphocytes. Since recent data have implicated the T lymphocyte as playing a critical role in chronic asthma, a number of investigators have evaluated cyclosporine in steroid-dependent asthma.[113,114] Most recently, Alexander[114] conducted a double-blind, placebo-controlled, crossover trial of cyclosporine (initial dose 5 mg/kg/day) or placebo for 12 weeks with a 2-week washout period. In 30 of 33 patients in the cyclosporine group, the peak expiratory flow rate and FEV_1 increased significantly and the frequency of disease exacerbations was 48% lower. Corticosteroid dosage reduction was not attempted in this study. The well-known side effects of cyclosporine include hypertension, hypertrichosis, neurological disturbances, and nephrotoxicity.

Leukotriene antagonists

The sulfidopeptide or cysteinyl leukotrienes (LTC4, LTD4, and LTE4), formerly known as the slow-reacting substance of anaphylaxis (SRS-A), are formed by the lipoxygenation of arachidonic acid by the enzyme 5-lipoxygenase.[115,116] Much data over the past 10 years suggest that the cysteinyl leukotrienes play a role in spontaneously occurring human asthma. These compounds, released by mast cells and eosinophils, have a variety of potent effects, including bronchoconstriction, increased permeability, and enhanced airway reactivity. The cysteinyl leukotrienes can be recovered from nasal secretions, bronchoalveolar lavage fluid, and urine of patients with asthma.[117,118]

A number of recently developed pharmacologic antagonists further support the role of leukotrienes in a number of models of human asthma. Specifically, potent competitive receptor antagonists to LTD4 inhibit asthmatic responses to allergens, exercise, cold dry air, and aspirin.[119–121]

A 5-lipoxygenase inhibitor, zileuton, was recently evaluated in the treatment of mild to moderate chronic asthma in a 4-week, placebo-controlled, parallel study.[122] A total of 139 asthma patients with an FEV_1 between 40% and 75%, who were not receiving other therapy, were randomized to receive zileuton 2.4 g/day or 1.6 g/day or placebo. Zileuton increased the FEV_1 by 14.6% within 1 hour of administration. In addition, after 4 weeks of zileuton therapy, there was a 13.4% increase in FEV_1 from baseline along with a reduction in symptoms and in the frequency of beta-agonist use. Cysteinyl leukotriene production, as reflected by recovery of LTE4 in the urine, decreased by 39% at the dose of 2.4 g/day. This study supports the notion that long-term inhibition of leukotriene synthesis at the 5-lipoxygenase level may produce a clinically relevant benefit. This agent was well tolerated, but long-term studies need to be performed.

UNRESOLVED ISSUES

Much new information has emerged from intensive research in asthma in the past 5 to 10 years. However, as evidenced by a recent consensus conference,[1] there are many unresolved questions regarding the fundamental factors involved in the

pathogenesis of asthma, the etiology of upward trends in morbidity and mortality of asthma, and the utility of newer therapeutic agents in the long-term management of asthma. How do genetic factors, atopic status, and environmental factors (including allergen exposure, viral infections, and atmospheric pollutants) interact to produce the familiar symptoms of the airway disease? Is asthma a single disorder with a unique cause or a syndrome of multiple disorders with several etiologic mechanisms? What are the critical and rate-limiting steps in the asthma inflammatory cascade? Also, what is the natural history of the disease, the significance of airway hyperreactivity in asymptomatic individuals, the impact of long-term anti-inflammatory therapy, and the toxicity of long-term therapy? Future therapeutic strategies will in large part depend on the answers to some of these unresolved issues.

REFERENCES

1. **National Heart, Lung, and Blood Institute, National Asthma Education Program.** Expert panel report. Guidelines for the diagnosis and management of asthma. J Allerg Clin Immunol 1991; **88:**425–534.
2. Asthma—United States, 1980-1990. MMWR 1992; **41:**733–735.
3. **Weiss KB, Gergen PJ, Hodgson TA.** An economic evaluation of asthma in the United States. N Engl J Med 1992; **326:**862–866.
4. **Hogg JC.** The pathology of asthma. Clin Chest Med 1984; **5:**567–571.
5. **Smith DL, Deshazo RD.** State of the art. Bronchoalveolar lavage in asthma: an update and perspective. Am Rev Respir Dis 1993; **148:**523–532.
6. **Djukanovic R, Roche WR, Wilson JW, et al.** Mucosal inflammation in asthma. Am Rev Respir Dis 1990; **142:**434–457.
7. **Beasley R, Roche WR, Roberts JA, et al.** Cellular events in the bronchi in mild asthma and after bronchial provocation. Am Rev Respir Dis 1989; **139:**806–817.
8. **Laitinen LA, Laitinen A, Haahtela T.** A comparative study of the effects of an inhaled corticosteroid, budesonide, and a β2-agonist, terbutaline on airway inflammation in newly diagnosed asthma: a randomized double-blind, parallel-group controlled trial. J Allergy Clin Immunol 1992; **90:**32–42.
9. **Djukanovic R, Wilson JW, Britten YM, et al.** Effect of an inhaled corticosteroid on airway inflammation and symptoms of asthma. Am Rev Respir Dis 1992; **145:**699.
10. **Jeffrey PK, Godfrey RW, Adelroth E, et al.** Effect of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. Am Rev Respir Dis 1992; **145:**890–899.
11. **Lungren R, Soderberg M, Horstedt P, et al.** Morphological studies on bronchial mucosal biopsies from asthmatics before and after ten years treatment with inhaled steroids. Eur Respir J 1988; **1:**883–889.
12. **Juniper EF, Kline PA, van Zieleshem MA, et al.** Long-term effects of budesonide on airway responsiveness and clinical asthma severity in inhaled steroid-dependent asthmatics. Eur Respir J 1990; **3:**1122–1127.
13. **Barnes PJ, Pederson S.** Efficacy and safety of inhaled corticosteroids in asthma. Am Rev Resp Dis 1993; **148:**S1–S26.
14. **McFadden ER, Gilbert IA.** Medical progress: asthma. N Engl J Med 1992; **327:**1928–1937.
15. **Haahtela T, Jarvinen M, Kava T, et al.** Comparison of a B_2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. N Engl J Med 1991; **325:**388–392.
16. **Kertjens HAM, Brand PLP, Hughes MD, et al.** A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. N Engl J Med 1992; **327:**1413–1419.
17. **Toogood JH.** High dose inhaled steroid therapy for therapy. J Allergy Clin Immunol 1989; **83:**528–536.
18. **Laursen LC, Taudorf E, Weeke B.** High-dose inhaled budesonide in treatment of severe steroid-dependent asthma. Eur J Respir Dis 1986; **68:**19–28.
19. **Tarlo SM, Broder I, Davies GM, et al.** Six-month double-blind controlled trial of high dose, concentrated beclomethasone dipropionate in the treatment of severe chronic asthma. Chest 1988; **93:**998–1002.
20. **Lipworth BJ.** Clinical pharmacology of corticosteroids in bronchial asthma. Pharmacol Ther 1993; **58:**173–209.
21. **Newman SP, Moren F, Pavia D, et al.** Deposition of pressurized suspension aerosols inhaled through extension devices. Am Rev Respir Dis 1981; **124:**317–320.
22. **Luengo M, Picado C, Del Rio L, et al.** Vertebral fractures in steroid dependent asthma and involutional osteoporosis: a comparative study. Thorax 1991; **46:**803–806.
23. **Murphy S, Kelly HW.** Cromolyn sodium: a review of mechanisms and clinical use in asthma. Drug Intell Clin Pharm 1987; **21:**22–35.
24. **Hoag JE, McFadden ER.** Long-term effect of cromolyn sodium on nonspecific bronchial hyperresponsiveness: a review. Ann Allergy 1991; **66:**53–63.
25. **Petty TL, Rollins DR, Christopher K, et al.** Cromolyn sodium is effective in adult chronic asthmatics. Am Rev Respir Dis 1989; **130:**694–701.
26. **Hambleton G, Weinberger M, Taylor J, et al.** Comparison of cromoglycate (cromolyn) and theophylline in controlling symptoms of chronic asthma. A collaborative study. Lancet 1977; **1:**381–385.
27. **Shapiro GG, Sharpe M, DeRoven TA, et al.** Cromolyn versus triamcinolone acetonide for children with moderate asthma. J Allerg Clin Immunol 1991; **88:**742–748.
28. **Toogood JH, Jennings B, Lefcol NM.** A clinical trial of combined cromolyn/beclomethasone treatment for chronic asthma. J Pediatr 1981; **67:**317–324.
29. **Edwards AM, Stevens MT.** The clinical efficacy of inhaled nedocromil sodium (Tilade) in the treatment of asthma. Eur Respir J 1993; **6:**35–41.
30. **Callaghan B, Teo NC, Clancy L.** Effects of the addition of nedocromil sodium to maintenance bronchodilator therapy in the management of chronic asthma. Chest 1992; **101:**787–792.
31. **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.
32. **DeJong JW, Teengs JP, Postma DS, van der Mark TW, Koeter GH, de Monchy JG.** Nedocromil sodium versus albuterol in the management of allergic asthma. Am J Respir Crit Care Med 1994; **149:**91–97.
33. **Geddes DM, Turner-Warnick M, Brewis RA, Davies RJ.** Nedocromil sodium workshop. Respir Med 1989; **82:**265–267. Editorial.
34. **O'Byrne RM.** Is nedocromil sodium effective treatment for asthma? Eur Respir J 1993; **6:**5–6. Editorial.
35. **Bel EH, Timmers MC, Hermans J, et al.** The long term effects of nedocromil sodium and beclomethasone dipropionate on bronchial responsiveness to methacholine in nonatopic asthmatic subjects. Am Rev Respir Dis 1990; **141:**21–28.

36. **Svendsen UG, Jorgensen H.** Inhaled nedocromil sodium as additional treatment to high dose inhaled corticosteroids in the management of bronchial asthma. Eur Respir J 1991; **4**:992–999.
37. **Wong CS, Cooper S, Britton JR, et al.** Steroid sparing effect of nedocromil sodium in asthmatic patients taking high doses of inhaled steroids. Thorax 1991; **46**:768P–769P.
38. **Robin ED, McCauley R.** Sudden cardiac death in bronchial asthma and inhaled beta-adrenergic agonists. Chest 1992; **101**:1699–1702.
39. **Nelson HS, Szeffler SJ, Martin RJ.** Regular inhaled beta-adrenergic agonists in the treatment of bronchial asthma: beneficial or detrimental? Am Rev Respir Dis 1991; **144**:249–250.
40. **Wilson JD, Sutherland DC, Thomas AC.** Has the change to beta-agonists combined with oral theophylline increased cases of total asthma? Lancet 1981; **1**:1235–1237.
41. **Grant IWB.** Asthma in New Zealand. Br Med J 1983; **286**:374–377.
42. **Sears MR, Taylor DR, Pring CG, et al.** Regular inhaled beta-agonist treatment in bronchial asthma. Lancet 1990; **336**:1391–1396.
43. **Spitzer WO, Suissa S,Ernest P, Horwitz RI, et al.** The use of β-agonists and the risk of death and near death from asthma. N Engl J Med 1992; **326**:501–506.
44. **Ernst P, Habbick B, Suissa S, et al.** Is the association between inhaled beta-agonist use and life-threatening asthma because of confounding by severity? Am Rev Respir Dis 1993; **148**:75–79.
45. **Mullen ML, Mullen B, Carey M.** The association between β-agonist use and death from asthma. JAMA 1993; **270**:1842–1845.
46. **Sheppard D.** Airway hyperresponsiveness: mechanisms in experimental models. Chest 1989; **96**:1165–1168.
47. **O'Bryne PM, Hargreave FE, Kirby JG.** Airway inflammation and hyperresponsiveness. Am Rev Resp Dis 1991; **143**:S35–S37.
48. **Rea HH, Sears MR, Beaglehole R, et al.** Lessons from the national asthma mortality study: circumstances surrounding death. N Z Med J 1987; **100**:10–13.
49. **Sly RM.** Mortality from asthma, 1974-1984. J Allergy Clin Immunol 1988; **82**:705–717.
50. **Benatar SR.** Fatal asthma. N Engl J Med 1986; **314**:423–429.
51. **Rea HH, Seragg R, Jackson R, et al.** A case-control study of deaths from asthma. Thorax 1986; **41**:833–839.
52. **Barger LW, Vollmer WM, Fleit RW, Buist AS.** Further investigation into the recent increase in asthma death rates: a review of 41 asthma deaths in Oregon in 1982. Ann Allergy 1988; **60**:31–39.
53. **Strunk RC.** Death due to asthma. Am Rev Respir Dis 1993; **148**:550–552.
54. **Weiss KB, Wagener Dk.** Changing patterns of asthma mortality: identifying target populations at high risk. JAMA 1990; **264**:1683–1687.
55. **Wasserfallen JB, Schaller MD, Feihl F, et al.** Sudden asphyxic asthma: a distinct entity? Am Rev Respir Dis 1990; **142**:108–111.
56. **Kallenbach JM, Frankel AH, Lapinsky SE, et al.** Determinants of near fatality in acute severe asthma. Am J Med 1993; **95**:265–272.
57. **Sur S, Crotty TB, Kephart GM, et al.** Sudden-onset fatal asthma. Am Rev Respir Dis 1993; **148**:713–719.
58. **Molfino NA, Nannini LJ, Rebuck AS, et al.** The fatality-prone asthmatic patients. Chest 1992; **101**:621–623.
59. **Barriot P, Riou B.** Prevention of fatal asthma. Chest 1987; **92**:460–466.
60. **Reid LM.** The presence or absence of bronchial mucous in fatal asthma. J Allergy Clin Immunol 1987; **80**:415–416.
61. **Colacone A, Afilado M, Wolkove N, et al.** A comparison of albuterol administered by metered dose inhaler (and holding chamber) or wet nebulizer in acute asthma. Chest 1993; **104**:835–841.
62. **Shim CS, Williams MH Jr.** Effect of bronchodilator administered by canister versus jet nebulizer. J Allergy Clin Immunol 1984; **73**:387–390.
63. **Turner JR, Corkery KJ, Eckman D, et al.** Equivalence of continuous flow nebulizer and metered dose inhaler with reservoir bag for treatment of acute air flow obstruction. Chest 1988; **93**:476–481.
64. **Moler FW, Hurwitz ME, Custer JR.** Improvement in clinical asthma score and $PaCO_2$ in children with severe asthma treated with continuously nebulized terbutaline. J Allergy Clin Immunol 1988; **81**:1101–1109.
65. **Chipps BE, Blackney DA, Black LE, et al.** Vortran high output extended aerosol respiratory therapy (HEART) for delivery of continuously nebulized terbutaline for the treatment of acute bronchospasm. Pediatric Asthma, Allergy and Immunology 1990; **4**:271–277.
66. **Colacone A, Wolkove N, Stern E, et al.** Continuous nebulization of albuterol (Salbutamol) in acute asthma. Chest 1990; **97**:693–697.
67. **Olshaker J, Jerrard D, Barish RA, et al.** The efficacy and safety of a continuous albuterol protocol for the treatment of acute adult asthma attacks. Am J Emerg Med 1993; **11**:131–133.
68. **Lin RY, Smith AJ, Hergenroeder P.** High serum albuterol levels and tachycardia in adult asthmatics treated with high-dose continuously aerosolized albuterol. Chest 1993; **103**:221–225.
69. **Portnoy J, Nadel G, Amado M, Willsie-Ediger S.** Continuous nebulization for status asthmaticus. Ann Allergy 1992; **69**:71–79.
70. **British Thoracic Society.** Guidelines for management of asthma in adults. Br Med J 1990; **301**:651–653.
71. **Rossing TH, Fanta CH, Goldstein, et al.** Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. Am Rev Respir Dis 1980; **122**:365–371.
72. **Siegel D, Sheppard D, Gelb A, et al.** Aminophylline increases the toxicity but not the efficacy of an inhaled beta-adrenergic agonist in the treatment of acute exacerbations of asthma. Am Rev Respir Dis 1985; **132**:283–286.
73. **Fanta CH, Rossing TH, McFAdden ER, Jr.** Treatment of acute asthma—is combination therapy with sympathomimetics and methylxanthines indicated? Am J Med 1986; **80**:5–10.
74. **Littenberg B.** Aminophylline treatment in severe, acute asthma: a meta-analysis. JAMA 1988; **259**:1678–1684.
75. **Self TH, Abou-Shala N, Burns R, et al.** Inhaler albuterol and oral prednisone therapy in hospitalized adult asthmatics. Does aminophylline add any benefit? Chest 1990; **98**:1317–1321.
76. **Wrenn K, Slovis CM, Murphy F, Greenberg RS.** Aminophylline therapy for acute bronchospastic disease in the emergency room. Ann Intern Med 1991; **115**:241–247.
77. **McFadden ER.** Methylxanthines in treatment of asthma: the rise, the fall, and the possible rise again. Ann Intern Med 1991; **115**:323–324. Editorial.
78. **Huang D, O'Brien RG, Harman E, et al.** Does aminophylline benefit adults admitted to the hospital for an acute exacerbation of asthma? Ann Intern Med 1993; **119**:1155–1160.
79. **DiGiulio GA, Kercsmar CM, Krug SE, et al.** Hospital treatment of asthma: lack of benefit from theophylline given in addition to nebulized albuterol and intravenously administered corticosteroid. J Pediatr 1993; **122**:464–469.
80. **Carter E, Cruz M, Chesrown S, et al.** Efficacy of intravenously administered theophylline in children hospitalized with severe asthma. J Pediatr 1993; **122**:470–476.
81. **Graft DF, Valentine MD.** Immunotherapy. In: Weiss EB, Stein M, editors. Bronchial asthma: mechanisms and therapeutics. Boston: Little, Brown and Company, 1993:934.
82. **Warner JO, Price JF, Soothill JF, Hey EN.** Controlled trial of hyposensitization to Dermatophagoides pteronyssinus in children with asthma. Lancet 1978; **2**:912–945.
83. **Bousquet J, Hejjaoui A, Clauzel AM, et al.** Specific immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. II. Prediction of efficacy of immunotherapy. J Allergy Clin Immunol 1988; **82**:971–977.
84. **Ortolani C, Pastorello E, Moss RB.** Grass pollen immunotherapy: a single year double-blind, placebo-controlled study in patients with grass pollen-induced asthma and rhinitis. J Allergy Clin Immunol 1984; **73**:283–290.

85. **Reid MJ, Moss RB, Hsu YP, Kwasnicki JM, Commerford TM, Nelson BL.** Seasonal asthma in northern California: allergic causes and efficacy of immunotherapy. J Allergy Clin Immunol 1986; **78:**590–600.
86. **Rak S, Lowhagen O, Venge P.** The effect of immunotherapy on bronchial hyper-responsiveness and eosinophilic cationic protein in pollen-allergic patients. J Allergy Clin Immunol 1988; **82:**470.
87. **VanMetre TE Jr, Marsh DG, Adkinson NF Jr.** Immunotherapy for cat asthma. J Allergy Clin Immunol 1988; **82:**1055–1068.
88. **Valovirta E, Viander M, Koivikko A, Vanto T, Ingeman L.** Immunotherapy in allergy to dog. Immunologic and clinical findings of a double-blind study. Ann Allergy 1986; **57:**173–179.
89. **Dreborg S, Agrell B, Foucard T, Kjellman NI, Koivikko A, Nilsson S.** A double-blind multicenter immunotherapy trial in children, using a purified and standardized *Cladosporium herbarum* preparation. I. Clinical results. Allergy 1984; **1:**131–140.
90. **Horst M, Hejjaoui A, Horst V, Michel FB, Bousquet J.** Double-blind placebo-controlled rush immunotherapy with a standardized *Alternaria* extract. J Allergy Clin Immunol 1990; **85:**460–472.
91. **Reed CE.** What we do and do not know about mold allergy and asthma. J Allergy Clin Immunol 1985; **76:**773–775.
92 **Abramson MJ, Puy RM, Weiner JM.** Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. Am J Respir Crit Care Med 1995; **151:** 969–974.
93. **Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC.** Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol 1987; **79:**660–677.
94. **Carmichael J, Paterson IC, Diaz P, et al.** Corticosteroid resistance in chronic asthma. Br Med J 1981; **282:**1419–1422.
95. **Dykewicz MS, Greenberger PA, Patterson R, et al.** Natural history of asthma in patients requiring long-term systemic corticosteroids. Arch Intern Med 1986; **146:**2369–2372.
96. **Corrigan CJ, Brown PH, Barnes NC, et al.** Glucocorticoid resistance in chronic asthma. Am Rev Respir Dis 1991; **144:**1016–1032.
97. **Mullarkey MF, Blumenstein BA, Andrade WP, et al.** Methotrexate in the treatment of corticosteroid dependent asthma. A double-blind crossover study. N Engl J Med 1988; **318:**603–606.
98. **Mullarkey MF, Lammert JK, Blumenstein BA.** Long-term methotrexate treatment in steroid dependent asthma. Ann Intern Med 1990; **112:**577–581.
99. **Dyer P, Vaughan T, Weber R.** Methotrexate in the treatment of steroid-dependent asthma. J Allergy Clin Immunol 1991; **88:**208–212.
100. **Shiner RJ, Nunn AJ, Chung KF, et al.** Randomized, double-blind, placebo controlled trial of methotrexate in steroid dependent asthma. Lancet 1990; **336:**137–140.
101. **Erzurum C, Leff JA, Cochran JE, et al.** Lack of benefit of methotrexate in severe steroid dependent asthma. A double-blind, placebo-controlled study. Ann Intern Med 1991; **114:**353–360.
102. **Coffey MJ, Sanders G, Eschenbacher WL, et al.** The role of methotrexate in the management of steroid-dependent asthma. Chest 1994; **105:**117–121.
103. **Bernstein DI, Bernstein IL, Bodenheimer SS, et al.** An open study of auranofin in the treatment of steroid dependent asthma. J Allergy Clin Immunol 1988; **81:**6–16.
104. **Nierop G, Gijzel WP, Bel EH, et al.** Auranofin in the treatment of steroid dependent asthma: a double blind study. Thorax 1992; **47:**349–354.
105. **Muranaka M, Miyamoto T, Shida T, et al.** Gold salts in the treatment of bronchial asthma—a double-blind study. Ann Allergy 1978; **40:**132–137.
106. **Klaustermeyer WB, Noritake DT, Kwong FK.** Chrysotherapy in the treatment of corticosteroid dependent asthma. J Allergy Clin Immunol 1987; **79:**720–725.
107. **Spector SL, Katz FH, Farr RS.** Troleandomycin: effectiveness in steroid dependent asthma. J Allergy Clin Immunol 1974; **54:**367–379.
108. **Szefler SJ, Rose JQ, Elliott EF, et al.** The effect of troleandomycin on methylprednisolone elimination. J Allergy Clin Immunol 1980; **66:**447–451.
109. **Zeiger RS, Schatz M, Sperling W, et al.** Efficacy of troleandomycin in outpatients with severe, corticosteroid-dependent asthma. J Allergy Clin Immunol 1980; **66:**438–446.
110. **Wald JA, Friedman BF, Farr RS.** An improved protocol for the use of troleandomycin in the treatment of steroid requiring asthma. J Allergy Clin Immunol 1986; **78:**36–43.
111. **Kamada AK, Hill MR, Ikhe DN, et al.** Efficacy and safety of low-dose troleandomycin therapy in children with severe, steroid-requiring asthma. J Allergy Clin Immunol 1993; **91:**873–882.
112. **Nelson HS, Hamilos DL, Corsello PR, et al.** A double-blind study of troleandomycin and methylprednisolone in asthmatic subjects who require daily corticosteroids. Am Rev Respir Dis 1993; **147:**398–404.
113. **Calderon E, Lockey RF, Bukantz SC, et al.** Is there a role for cyclosporine in asthma? J Allergy Clin Immunol 1992; **89:**629–636.
114. **Alexander AG, Barnes NC, Kay AB.** Trial of cyclosporin in corticosteroid dependent chronic severe asthma. Lancet 1992; **339:**324–327.
115. **Samuelsson B, Dahlen SE, Lindgren JA, Rouzer CA, Serhan CN.** Leukotrienes and lipoxins: structures, biosynthesis, and biological effects. Science 1987; **237:**1171–1176.
116. **Drazen JM.** Inhalation challenge with sulfidopeptide leukotrienes in human subjects. Chest 1986; **89:**414–419.
117. **Smith CM, Hawksworth, Thien FCK, et al.** Urinary leukotriene E_4 in bronchial asthma. Eur Respir J 1992; **5:**693–699.
118. **Drazen JM, O'Brien JB, Sparrow D, et al.** Recovery of leukotriene E_4 from the urine of patients with airway obstruction. Am Rev Respir Dis 1992; **146:**104–108.
119. **Dahlen B, Kumlin M, Margolskee DJ, et al.** The leukotriene-receptor antagonist MK-0679 blocks airway obstruction induced by inhaled lysine-aspirin in aspirin-sensitive asthmatics. Eur Respir J 1993; **6:**1018–1026.
120. **Taylor IK, O'Shaughnessy KM, Fuller RW, Dollery CT.** Effect of cysteinyl-leukotriene receptor antagonist ICI 204.219 on allergen-induced bronchoconstriction and airway hyperreactivity in atopic subjects. Lancet 1991; **337:**690–694.
121. **Israel E, Dermarkarian R, Rosenberg M, et al.** The effects of 5-lipoxygenase inhibitor on asthma induced by cold, dry air. N Engl J Med 1990; **323:**1740–1744.
122. **Israel E, Rubin P, Kemp JP, et al.** The effect of inhibition of 5-lipoxygenase by zileuton in mild-to-moderate asthma. Ann Intern Med 1993; **119:**1059–1066.