AllergyWatch®

A Synopsis of Allergy and Asthma Literature, Resulting from an Unbiased, Comprehensive Review of Seventeen Major Medical Journals.

A Publication of The American College of Allergy, Asthma & Immunology

Volume 3, Number 6 November-December 2001

Growth Concerns Shouldn't Interfere with Inhaled Steroid Therapy for Asthma

THE use of inhaled corticosteroids to treat childhood asthma has increased in recent years. Yet pediatricians may continue to question the safety of this treatment, particularly because of concern over potential adverse effects on growth. Evidence regarding the effects of inhaled corticosteroid therapy for asthma on growth in children is reviewed.

Low-dose corticosteroids are a highly effective treatment for asthma--most studies show no significant additional effect on symptoms or lung function at steroid doses higher than 100 µg/d. The risk of adverse effects, including growth effects, can be reduced by selecting an inhaler-drug combination with a high therapeutic index and by individualizing the dose to the severity of disease. Data from studies of one inhaler-drug combination may not apply to other combinations, however. Large, long-term studies are needed to assess the rates of clinically significant adverse effects of inhaled steroids at the doses commonly used for patients of a given age and disease severity.

Studies of the effects of inhaled corticosteroids on short- and intermediate-term growth suggest that most of the adverse growth effects occur near the start of treatment: within the first 3 months. Analysis of the expected effects of treatment on final adult height suggest a possible time-dependent effect. However, studies of 1-year growth provide no useful information for predicting growth over longer periods, nor for predicting final adult height. Children receiving high doses of inhaled corticosteroids have slower growth. If treatment continues, they may be a centimeter or two shorter than their peers, but final adult height is unchanged. By contrast, uncontrolled asthma itself can adversely affect on adult height.

Available data support the safety and efficacy of low-dose inhaled corticosteroid therapy for children with asthma. Despite the low rate of adverse effects--including growth effects--some physicians hesitate to prescribe these beneficial medications. In reality, failure to use inhaled steroids leads to poorer disease control and thus to poorer growth, among other negative consequences. ➤➤

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The American College of Allergy, Asthma & Immunology expresses its appreciation to Aventis Pharmaceuticals Inc.for its unrestricted grant in support of the publication of *AllergyWatch*.®

The following journals have been selected as the primary focus of review in the preparation of materials within "AllergyWatch®".

- Annals of Allergy, Asthma and Immunology
- Journal of Allergy and Clinical Immunology
- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- Mayo Clinic Proceedings

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COMMENT: *This outstanding analytical review covers the published data that have led to concern about growth in children with asthma who are treated with inhaled corticosteroids. The author places a lot of information from growth studies into a balanced perspective for the clinician. The message is that mild to moderate childhood asthma responds well to low-dose inhaled corticosteroids without discernible effects on growth.*
J.B.-M.

Pedersen S: Do inhaled corticosteroids inhibit growth in children?
Am J Respir Crit Care Med 164:521-535, 2001. ♦♦

Omalizumab Is Beneficial in Severe, Steroid-Dependent Allergic Asthma

GIVEN the key role of IgE in the pathogenesis of allergy, it is hoped that anti-IgE monoclonal antibodies will provide a useful new approach to asthma treatment. The anti-IgE recombinant human monoclonal antibody omalizumab (rhuMAb-E25) blocks free IgE from interacting with mast cells and basophils. Omalizumab was evaluated for safety and efficacy in the treatment of severe allergic asthma that was uncontrolled by inhaled corticosteroids.

The randomized, double-blind, placebo-controlled trial included 525 adolescent to adult patients with severe allergic asthma requiring daily inhaled corticosteroid therapy. All patients had had asthma for at least 1 year with a positive skin prick test to common allergens, elevated total serum IgE, and FEV_1 reversibility of at least 12% with albuterol. The active- treatment group received subcutaneous omalizumab once or twice monthly, based on their IgE level and body weight. This yielded a dosage of about 0.016 mg/kg IgE every 4 weeks. Inhaled corticosteroid dosage was held stable for the first 16 weeks of the study, then tapered over the subsequent 12 weeks.

Dropout rates were 7% in the omalizumab group and 13% in the placebo group; withdrawals due to unsatisfactory treatment effect were more frequent in the placebo group. With corticosteroid dosage held stable, the exacerbation rate was 15% with omalizumab vs 23% with placebo. Number of exacerbations per patient and duration of exacerbations were also less with omalizumab.

During the steroid-tapering phase, patients receiving omalizumab had greater reductions in beclomethasone dipropionate dose. Thirty-seven percent of patients in the omalizumab group were able to discontinue inhaled corticosteroids, compared with 19% in the placebo group. Symptom scores, pulmonary function test results, and rescue β-agonist use also decreased with omalizumab. In both groups, adverse events were generally mild to moderate.

Omalizumab reduces asthma exacerbations among patients with severe, steroid-dependent allergic asthma. This anti-IgE monoclonal antibody also reduces dependence on inhaled corticosteroids, and eliminates the need for steroids in a significant number of patients. Omalizumab is a beneficial treatment for a difficult-to-manage group of patients.

COMMENT: *In this large phase III study, steroid-dependent asthmatics using omalizumab subcutaneously had improved control of their asthma. Besides demonstrating improvements in asthma symptoms and pulmonary function tests, they had reductions in the use of rescue medications and in inhaled corticosteroid requirements. It was particularly impressive that almost twice as many patients on omalizumab could discontinue their inhaled corticosteroids compared to controls. Now, can anyone help me pronounce the name for this product?*
S. M. F.

Busse W, Corren J, Lanier BQ, et al: Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma.
J Allergy Clin Immunol 108:184-190, 2001. ♦♦

Steroid-insensitive Nasal Polyposis Linked to GRβ Overexpression

NASAL polyps are associated with eosinophilic chronic inflammation of the respiratory mucosa, which may not respond even to prolonged treatment with topical corticosteroids. Previous studies have suggested that the mechanism of steroid-unresponsiveness in asthma may involve the glucocorticoid receptor splice variant GRβ. This study examined GRβ expression in 10 patients with nasal polyposis.

Middle turbinate nasal mucosal biopsy specimens were obtained from these patients before and 4 weeks after treatment with topical fluticasone propionate, as well as from 6 normal controls. The biopsy specimens were studied by immunostaining for inflammatory cell markers and GRβ.

Two of the patients with nasal polyposis were considered symptomatic "failures" of fluticasone therapy. In the nasal polyp specimens, expression of GRβ was noted almost exclusively in T lymphocytes, eosinophils, and macrophages. Nasal polyp specimens were rated as sensitive or insensitive to fluticasone, based on whether eosinophil numbers were reduced. The fluticasone-insensitive polyps had a higher proportion of GRβ-positive inflammatory cells, compared with fluticasone-sensitive polyps. Fluticasone insensitivity was also associated with a higher ratio of GRβ-positive to GRα-positive cells and with higher numbers of GRβ-positive eosinophils and macrophages.

Inflammatory cells from nasal polyps overexpress GRβ, especially in T lymphocytes, eosinophils, and macrophages. In nasal polyposis as in other conditions, GRβ overexpression may be an indicator of steroid insensitivity. The authors discuss the potential effects of GRβ overexpression on eosinophil function, along with other potential mechanisms of steroid resistance.

COMMENT: *Clinically, nasal polyps can be exquisitely sensitive--or frustratingly insensitive--to corticosteroids. Cellular GRs come in α and β forms, the latter being functionally incompetent. Overexpression of GRβ on inflammatory cells has been postulated as a mechanism of steroid resistance in asthma. So too, it seems, in nasal polyposis, as shown by this study. T cells, macrophages, and eosinophils from steroid-resistant polyps expressed significantly more dysfunctional GRβ receptors.*

R. J. M.

Hamilos DL, Leung DYM, Muro S, et al: GRβ expression in nasal polyp inflammatory cells and its relationship to the anti-inflammatory effects of intranasal fluticasone.

J Allergy Clin Immunol 108:59-68, 2001. ♦♦

Food-Dependent Exercise-Induced Anaphylaxis: a Diagnostic Approach

PATIENTS with food-dependent exercise-induced anaphylaxis (FDEIAn) have reactions provoked by ingestion of specific foods when they exercise afterward. The mechanism of these reactions is unknown, although the finding of skin test or RAST positivity suggests an IgE-dependent mechanism. This study evaluates a diagnostic protocol for identifying the foods responsible for FDEIAn, including skin tests and a specific IgE assay.

The study included 54 patients referred to an allergy unit for evaluation of FDEIAn episodes. A detailed history was collected from each patient. Thirty-three had a family history of atopy, 9 had urticaria or angioedema unrelated to food or exercise, and 8 had had adverse reactions to food without exercise. The episodes occurred 30 to 120 minutes after food ingestion. Forty-eight patients suspected a specific food of being involved, most commonly tomatoes, wheat, and peanuts. Symptoms included pruritus in 94% of patients, urticaria in 85%, angioedema in 83%, flushing in 74%, dyspnea in 70%, GI symptoms in 35%, hypotension in 33%, and upper respiratory symptoms in 30%.

Each patient underwent skin-prick testing (SPT) with 26 different food allergens, as well as prick-plus-prick tests for 15 fresh foods including 9 of those evaluated on SPT. In vitro RAST assay for 31 food allergens was used to measure specific IgE levels. Tests showed positive responses to at least one food in 52 patients, including 22 patients who responded to more than 20 different foods. Just 2 patients had no positive test results. Sensitivities varied among the tests; each revealed some positive reactions that were undetected by the others.

Forty-eight patients were classified as having probable specific FDEIAn and 6 as having nonspecific reactions. Patients in the former group were advised to avoid all foods to which they tested positive for 4 hours before exercising. None of the 43 patients followed up had another reaction.

The results support a combined in vivo/in vitro approach to testing for testing for food sensitivity in patients with FDEIAn. Many different sensitivities may be identified in patients with this complex type of food allergy. The CAP in vitro test may be more sensitive than in vivo tests; the PRIST assay appears not to be helpful. Avoiding the implicated foods before exercising can prevent future reactions in patients with specific FDEIAn.

COMMENT: *In this study 54 patients with FDEIAn performed postprandial exercise challenges after extensive specific IgE testing. The results confirm many previous observations regarding this fascinating disease. Perhaps the most important observation was that avoidance of the foods testing positive by skin testing and/or CAP serologic testing for 4 hours prior to exercise completely prevented symptoms. The CAP method was more sensitive than skin tests in some cases and should be considered when the specific causative food is not obvious by history and initial skin testing.*

S. A. T.

Romano A, Di Fonso M, Giuffreda F, et al: Food-dependent exercise-induced anaphylaxis: clinical and laboratory findings in 54 subjects.

Int Arch Allergy Immunol 125:264-272, 2001. ♦♦

Specific Immunotherapy Reduces Rate of Polysensitization

SPECIFIC immunotherapy (SIT) is of documented benefit in the treatment of respiratory allergic disease, offering long-term modification of the natural history of the disease. Aside from one study in children, few reports have described the ability of SIT to reduce sensitization to new allergens. This retrospective study evaluated the effects of SIT on the development of polysensitization in a large group of initially monosensitized patients.

The study included a total of 8,396 patients with allergic rhinitis and or mild to moderate asthma who were at least 14 years old and had documented monosensitization to one respiratory allergen, excluding cat. Of these, 7,182 patients received 4 years of SIT, using native allergens prepared for injective depot treatment. The remaining 1,214 patients received anti-allergic medications only. In both groups, follow-up included skin-prick testing with a standard panel of allergens as well as total and specific IgE measurements.

At 4 years' follow-up, about 24% of patients in the SIT group had become sensitized to additional allergens, compared with 68% in the control group. By 7 years, polysensitization rates were 27% vs 77%, respectively. Patients with asthma were more likely to develop polysensitization than those with rhinitis only. Patients in the SIT group had a 24% reduction in specific IgE, compared with a 24% increase in the control group. Specific IgE levels decreased by 18% with SIT compared to a 14% increase in controls.

This large study of adolescent to adult monosensitized patients suggests that SIT reduces the development of polysensitization. Patients receiving SIT also show significant reductions in total and specific IgE. The results have important implications for the cost/benefit ratio of SIT.

COMMENT: *Progression from monosensitization to polysensitization is an anticipated event among atopic individuals. A previous study in children concluded that this progression could be inhibited by conventional immunotherapy. The mean age in the present study was 22 years, and it reported the same result. The retrospective design may have overestimated the number of monosensitized subjects at the time immunotherapy was started. However, the result is impressive, given the very large number of patients included. The utility of this information to the average allergy practice in the United States is unclear, as most patients we evaluate are not monosensitized.*
S. A. T.

Purello-D'Ambrosio F, Gangemi S, Merendino RA, et al: Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study.
Clin Exp Allergy 31:1295-1302, 2001.

Aspirin-sensitive Asthma Patients Don't Cross-React With COX-2 Inhibitor

PATIENTS with aspirin-sensitive respiratory disease may show cross-reactivity to any nonsteroidal anti-inflammatory drug (NSAID) that inhibits the cyclo-oxygenase (COX) enzymes, COX-1 and COX-2. Some recently introduced arthritis drugs are selective COX-2 inhibitors. This study examined whether aspirin-sensitive asthma patients cross-react with the COX-2 inhibitor rofecoxib.

The study included 60 patients with aspirin-sensitive asthma. In a clinical research center, the patients received double-blind, placebo-controlled oral challenges with rofecoxib in clinical doses of 12.5 and 25.0 mg. Two placebo challenges were given as well. The next day, a single-blind oral aspirin challenge was given to confirm sensitivity.

None of the patients responded to rofecoxib challenge. There were no symptoms, no naso-ocular reactions, and no changes in FEV_1. In contrast, all patients reacted to aspirin, with a mean provoking dose of 61 mg.

The findings in this statistically significant sample of aspirin-sensitive asthma patients show no cross-reactivity to the selective COX-2 inhibitor rofecoxib. The results support the safety of prescribing rofecoxib to patients with aspirin-sensitive respiratory disease. The findings also strengthen the theory that COX-1 inhibition is the triggering event in aspirin-induced respiratory reactions.

COMMENT: *Some people with asthma are known to develop severe exacerbations triggered by ingestion of aspirin, as well as by NSAIDs that inhibit both forms of the enzyme cyclo-oxygenase: COX-1 and COX-2. COX-1 is the main source of PGE_2, a protective prostaglandin. COX-2 selectivity would logically not be expected to trigger asthma--and this is exactly what the authors convincingly prove in 60 aspirin-sensitive patients challenged with rofecoxib (Vioxx). (Celecoxib was not studied. See* AllergyWatch *July/Aug 2001, p. 2.)*
R. J. M.

Stevenson DD, Simon RA: Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma.
J Allergy Clin Immunol 108:47-51, 2001. ♦♦

Honeybee Venom Immunotherapy: Results in a Patient with Large Local Reactions

UP to 17% of the general population experience large local reactions to inadvertent Hymenoptera stings. However, because these reactions are non-life-threatening, such individuals are not generally considered for venom immunotherapy. This report describes the successful use of venom IT in a patient who developed new sensitization to honeybee venom (HBV).

The previous year, the 47-year-old patient had participated as a nonatopic control in an allergy research trial, which included skin-testing to HBV and other common allergens. Subsequently, he moved to a home next to a farm with beehives, where he developed progressively larger local reactions in response to honeybee field stings. These included a very painful 62 cm local reaction with swelling of the entire arm after a sting to his forefinger, which took more than a month to resolve. ➤➤

Fearing a systemic reaction, the patient requested venom IT. Before therapy, an intentional bee sting challenge resulted in a 11.4 cm wheal with erythema and several weeks of edema. The patient received a rapidly escalating course of venom IT, reaching maintenance doses in 7 weeks. A 7-month post-maintenance sting challenge caused only a 3 cm area of erythema, with no wheal and no late-phase response. After 13 months of maintenance therapy, the patient had no visible reaction to a field sting. Measurement of HBV-specific antibodies showed a 100-fold reduction in venom skin reactivity.

In contrast to current practice guidelines, this case report supports the use of venom IT for patients with large local reactions to honeybee stings who are at risk for further stings. As for IT to other common allergens, the primary indication for venom IT in such cases would be to reduce morbidity. The potential for venom IT to produce large local reactions in allergic subjects remains unclear.

COMMENT: *This is a well-described report of an immunologic and clinical response to venom immunotherapy in a subject with insect hypersensitivity characterized by a very large local reaction. Practice guidelines do not recommend evaluation or treatment in this situation because the insect allergy is not life-threatening. The question posed by the authors is whether there should be latitude to consider quality of life, peace of mind, or morbidity reduction in nonanaphylactic, non-life-threatening insect hypersensitivity. Certainly immunotherapy is used for allergic rhinitis with these justifications, so why not severe, large local reactions to stinging insects? Additional proof of immunotherapy efficacy in large, local insect reactions is needed before general recommendations can be made.*

D. K. L.

Hamilton RG, Golden DBK, Kagey-Sobotka A, Lichtenstein LM: Case report of venom immunotherapy for a patient with large local reactions.

Ann Allergy Asthma Immunol 87:134-137, 2001. ♦♦

Meta-analysis Assesses Dose-response Relation of Inhaled Fluticasone

CURRENT recommendations as to the proper inhaled fluticasone propionate dosage to treat asthma are not based on strong scientific data on the clinically significant dose-response relationship. A meta-analysis was performed to assess the dose-response relationship of inhaled fluticasone for adolescent and adult patients with asthma.

The analysis included data from eight randomized, placebo-controlled clinical trials, comprising 2,324 adolescent and adult asthma patients, mean age 33 years. The studies lasted 6 to 12 weeks and were published between 1994 and 1998. All used at least two different fluticasone doses and at least one asthma outcome measure, such as FEV_1, peak expiratory flow, β-agonist use, or exacerbation rate.

Fluticasone doses used in the study ranged from 50 to 1,000 μg/d. All studies included a 200 μg/d dose; there were relatively few data on doses of 500 μg/d or greater. The raw data suggested a plateau in the dose-response curve starting at 100 to 200 μg/d and peaking by 500 μg/d. A fluticasone dose of 70 to 170 μg/d provided 80% of the benefit of a 1,000 μg/d dose, while a dose of 100 to 250 μg/d provided 90% of the benefit.

The available data suggest that an inhaled fluticasone dosage of 100 to 250 μg/d will deliver most of the treatment benefit in adolescent and adult patients with asthma. A 500 μg/d dosage appears to provide the maximal effect, although there are few data on fluticasone doses higher than this level. The findings support the benefits of adding a long-acting β-agonist to inhaled corticosteroid therapy, rather than increasing the inhaled steroid dose.

COMMENT: *What is the optimal dose of inhaled corticosteroids (ICS) for our asthmatic patients? Others have shown a plateau in the dose response for several ICS products. This meta-analysis clearly demonstrates that the plateau for fluticasone begins between 100 and 200 μg/d and peaks at 500 μg/d. The British Thoracic Society currently recommends a fluticasone dosage range of 400 to 1,000 μg/d. Our National Heart, Lung and Blood Institute guidelines recommend these dosages for patients with moderate or severe persistent asthma. Both the authors and the accompanying editorial recommend a re-evaluation of the proper dosing for ICS and encourage access to more detailed data from pharmaceutical companies to help determine the optimal dose for our patients.*

S. M. F.

Holt S, Suder A, Weatherall M, et al: Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis.

BMJ 323:1-8, 2001. ♦♦

Randomized Trial Supports Fluticasone/Salmeterol Over Montelukast in Persistent Asthma

TRADITIONALLY, combination approaches have been needed to treat both bronchoconstriction and the underlying inflammation in patients with asthma. This study compared two approaches to initial maintenance therapy for patients with persistent asthma: a combination of fluticasone propionate and salmeterol or oral treatment with the leukotriene receptor antagonist montelukast.

The multicenter, randomized, double-blind trial included 423 patients with asthma, aged 15 years or older, who remained symptomatic despite short-acting β_2-agonist therapy. Eligibility requirements included the need for rescue albuterol on at least 5 of 7 days during the previous week. Patients were randomized to receive either combination therapy, consisting of fluticasone propionate 100 μg and salmeterol 50 μg twice daily, administered via Diskus inhaler; or oral therapy with montelukast, 10 mg once daily. The fluticasone/sal- ➤➤

meterol group received placebo capsules, while the montelukast group received a placebo inhaler.

After 12 weeks of treatment, patients in the fluticasone/salmeterol group had a 23% increase in FEV_1, compared with an 11% increase in the montelukast group. Improvements in forced expiratory flow at 25 to 75 seconds were 53% vs 23%, respectively. The combination therapy group also had significantly greater improvements in morning and evening peak expiratory flow and in percentage of days free from symptoms, rescue medications, and nighttime awakenings. The two treatments were similarly well tolerated.

Combination therapy with twice-daily inhaled fluticasone and salmeterol is superior to once-daily oral montelukast in patients with persistent asthma on short-acting β_2-agonists. The combination approach, addressing both bronchoconstriction and inflammation, is advantageous in terms of pulmonary function, asthma symptoms, rescue medication use, and other key outcomes.

COMMENT: *By using the combination of salmeterol and fluticasone for patients symptomatic on short-acting β_2-agonists alone, the investigators bypassed the usual first-step maintenance treatment with an inhaled corticosteroid alone. This may have been justified by the severity of asthma in these patients who were, on average, symptomatic on about 96% of days. Montelukast may still be the best-choice initial maintenance therapy for some patients with milder asthma, when you consider both drug efficacy and the likelihood of patient compliance.*
J. R. B.

Calhoun WJ, Nelson HS, Nathan RA, et al: Comparison of fluticasone propionate-salmeterol combination therapy and montelukast in patients who are symptomatic on short-acting β_2-agonists alone.
Am J Respir Crit Care Med 164:759-763, 2001. ♦♦

Ragweed-specific Immunostimulatory Sequence Shifts from Th2 to Th1 Profile In Vitro

RECENT reports have described the effects of bacterially derived immunostimulatory sequences (ISSs) of DNA in activating the innate immune system of mammals, leading to the development of Th1-type cells. This in vitro study examined the ability of ISSs to alter the cytokine profile of allergen-stimulated blood cells from patients with allergy.

Peripheral blood mononuclear cells (PBMCs) were obtained from patients with confirmed allergy to short ragweed. Using a specific 22-base ISS and the immunodominant ragweed allergen Amb a 1, the investigators created a ragweed protein-linked ISS (PLI). When PBMCs were exposed to the PLI, their dominant allergen-induced Th2 profile was reversed. In its place, an enhanced Th1-type immunity developed, associated with increased levels of interferon-γ and interleukin-2. Allergen-specific T cell proliferation increased as well. In a further experiment, PLI exhibited cytokine-modulating properties even in cells with prolonged prestimulation with Amb a 1.

These in vitro results show that a ragweed PLI can alter the immune profile of PBMCs from a Th2 to a Th1 profile. Its cytokine-modulating activity, together with its reduced allergenicity, suggest that this ragweed PLI could have important advantages for use in allergen immunotherapy.

COMMENT: *One of the mechanisms of allergen immunotherapy is probably conversion of the patient's dominant immune response profile from Th2- to Th1-type. In the future, immunotherapy might be enhanced by presenting the specific antigen linked to fragments of bacterial DNA called "immunostimulatory sequences." The resulting protein-linked immunostimulant was used in vitro in this study to successfully convert blood cells from allergic subjects to a Th1 cytokine profile in an antigen-specific manner. Phase I clinical studies are underway.*
R. J. M.

Marshall JD, Abtahi S, Eiden JJ, et al: Immunostimulatory sequence DNA linked to the Amb a 1 allergen promotes T_{H1} cytokine expression while downregulating T_{H2} cytokine expression in PBMCs from human patients with ragweed allergy.
J Allergy Clin Immunol 108:191-197, 2001. ♦♦

Skin Test Results in Penicillin Allergy: 15-Year Analysis

Allergic reactions to β-lactam drugs continue to be a frequent cause of adverse drug reactions. However, penicillin is no longer the most commonly used β-lactam drug; patterns of reactions have changed as new chemical structures become available. Findings from a large data base of patients with allergy to penicillins are reported, including trends from the 1980s to the mid-1990s.

The analysis included 290 patients with immediate allergic reactions to a penicillin derivative. Patients with nonimmediate reactions were excluded, as were those with reactions to cephalosporins, monolactams, and other β-lactams. Investigations included skin testing with major and minor determinants of benzylpenicillin (BPO/MDM), amoxicillin, and ampicillin and in vitro measurements of specific IgE.

The clinical history was consistent with anaphylaxis in 71% of patients and urticaria or angioedema in 29%. Sixty-five percent of reactions were to amoxicillin. The next most frequent category, 15%, was "unrecalled penicillin"--ie, patients who reported penicillin allergy but were uncertain of the specific agent involved. Only 3% of reactions were to BPO.

Seventy percent of patients had a positive skin test to at least one determinant, most often amoxicillin. Overall, 42% of patients tested positive to determinants generated from BPO, while 58% were "selective responders."

Findings in a large group of patients with immediate allergic reactions to penicillin suggest that ➤➤

skin tests to BPO are less sensitive than previously reported. Rather, the pattern has shifted to increased representation of minor determinants, particularly amoxicillin. Anaphylactic reactions to penicillin outnumber urticarial reactions by more than two to one, which may explain the increased positivity of minor determinants. Increased caution is needed when performing penicillin skin tests.

COMMENT: *Hypersensitivity to the β-lactams remains the most common IgE-mediated drug reaction. This group of European investigators studied a large group of β-lactam-sensitive patients over the past 15 years and elucidated several important clinical observations. First, 70% of clinical reactions to the β-lactams that are anaphylactic reactions relate to minor determinants, mostly amoxicillin. Second, a negative skin test to BPO and minor determinants did not exclude a clinically significant reaction in 30% of cases where controlled administration was required to confirm the diagnosis. Since there is considerable variability of response among different populations, further similar studies should be conducted in North America.*
E. J. B.
Torrees MJ, Romano A, Mayorga C, et al: Diagnostic evaluation of a large group of patients with immediate allergy to penicillins: the role of skin testing.
Allergy 56:850-856, 2001. ♦♦

Doubled Dose of Immunoglobulin Reduces Infection Rate in Hypogammaglobulinemia

HYPOGAMMAGLOBULINEMIA leaves patients at risk of recurrent infections, the frequency and severity of which are reduced by immunoglobulin therapy. However, even with current IV immunoglobulin regimens, infections may continue. This randomized trial evaluated the effects of doubling the standard dose of IV immunoglobulin in patients with primary hypogammaglobulinemia.

The study included 43 patients with primary hypogammaglobulinemia from 15 Dutch clinics. Patients were randomized to receive either 9 months of standard-dose immunoglobulin therapy (300 mg/kg every 4 weeks in adults, 40 mg/kg every 4 weeks in children) or a double-dose regimen. Both treatments were followed by a 3-month washout period, after which the patients were crossed over to the other regimen. The effects of treatment on the number and duration of infections were compared, along with secondary outcomes.

Forty-one patients completed the trial. Total number of infections was 3.5 per patient with standard-dose immunoglobulin therapy vs 2.5 with the double dose. Median duration of infections was 33 vs 21 days, respectively. While receiving double-dose therapy, the patients had a significant increase in their trough IgG levels. The two regimens were similar in terms of incidence and types of side effects.

Doubling the standard dose of immunoglobulin significantly reduces the rate and severity of infections in patients with primary hypogammaglobulinemia. The authors propose an approach to individualizing the immunoglobulin dosage, based on patients' IgG levels and number of infections.

COMMENT: *The development of γ-globulin preparations suitable for IV administration permitted replacement or treatment with physiologic or supraphysiologic doses of globulin. The clinical question that arose was, if a little is good is more better? Or, how much is enough? This paper, along with another showing a reduction in chronic lung disease with greater doses of IV γ-globulin, supports an increased maintenance dosage. The question of the cost-benefit must be answered before we can accept that a reduction of one infection per 9 months justifies a 100% dose and cost increase in γ-globulin therapy.*
D. K. L.
Eljkhout HW, van der Meer JWM, Kallenberg GCM, et al: The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia: a randomized, double-blind, multicenter crossover trial.
Ann Intern Med 135:165-174, 2001. ♦♦

Allergenic When Wet: Grass Pollens Release Subcellular Particles After Hydration

INTACT grass pollens are too large to reach the deeper airways. Recent studies have suggested that subcellular grass pollen particles may be the source of allergen leading to pollen-induced asthma attacks. This study examined whether pollen of the sweet-grass family releases such allergen-bearing particles in response to hydration, as previously demonstrated for ryegrass.

The investigators performed scanning electron microscopic examination of pollen from various species of Poaceae grasses after hydration in distilled water. When hydrated, fresh pollens discharged significant amounts of cytoplasmic material, which proved on immunogold labeling studies to contain group 1 and 5 allergens. Discharge of these sub-micronic particles was significantly reduced for pollens that had been stored for 1 month. The findings were similar for all 6 Poaceae species investigated.

Fresh Poaceae pollens release allergen-containing respirable particles when wet. This mechanism of allergen release could account for how subcellular pollen particles gain access to the lower airways, and thus explain the occurrence of grass pollen-induced asthma attacks after a rainfall. It remains uncertain why some pollen species expel cytoplasmic particles while others do not.

COMMENT: *It is an old husbands' tale that allergy symptoms decrease after rainfall. How then to explain the* increased *incidence of asthma after rainfall during grass pollen season? The size of grass pollen grains makes them unlikely to be respirable. This study* ➤➤

confirms the suspicion that sub-micronic particles bearing allergens are released from the cytoplasm of sweetgrass pollen after hydration. The electron-micrographs of this release are striking. Birch pollen does not exhibit this phenomenon.
R. J. M.
Grote M, Vrtala S, Niederberger V, et al: Release of allergen-bearing cytoplasm from hydrated pollen: a mechanism common to a variety of grass (Poaceae) species revealed by electron microscopy.
J Allergy Clin Immunol 108:109-115, 2001. ♦♦

Modifiable Risk Factors for Asthma in Preschool Children Identified

PUBLIC health strategies to prevent asthma require data on risk factors. Although much is known about asthma risk factors in school-age children, there is little information on the relevant risk factors at younger ages. This epidemiologic study assessed risk factors for asthma among preschool-age children in Australia.

The cross-sectional study included the parents of 3- to 5-year old children living in two cities in New South Wales, Australia: 383 from Lismore, a coastal city with a humid climate; and 591 from Wagga Wagga, an inland city with a dry climate. A questionnaire was used to gather data on asthma, respiratory symptoms, and putative risk factors. Children were classified as having "recent asthma" if they had been diagnosed with asthma, and had had cough or wheezing and used asthma medications within the previous year. Skin prick testing was performed in a subsample of 650 children.

Twenty-two percent of the Lismore sample and 18% of the Wagga Wagga sample had recent asthma. Factors significantly associated with recent asthma included atopy, odds ratio (OR) 2.35; parental history of asthma, OR 2.05; serious respiratory infection during the first 2 years of life, OR 1.93; and high intake of polyunsaturated fats, OR 2.03. Children who had been breast fed were less likely to develop asthma, as were those with three or more older siblings. The risks associated with maternal vs paternal atopy were similar. There was no association with parental smoking, during or after pregnancy.

Risk factors for asthma among preschool-age children are identified, along with some protective factors. Efforts to reduce dietary consumption of polyunsaturated fats and to promote breast-feeding may help to prevent the onset of asthma during early childhood.

COMMENT: *There is mounting evidence that the prevalence of asthma and allergic disease is increasing worldwide. A number of risk factors have been identified. Ideally, to prevent development of asthma, strategies to modify known risk factors need to be developed. This Australian study of preschool children found that atopy, the consumption of fatty acids, and the absence of older siblings have a significant association with recent asthma, and that breast-feeding is associated with a decreased risk of asthma. If such risk factors can be confirmed, they will provide the substrate for future preventive trials.*
E. J. B.
Haby MM, Peat JK, Marks GB, et al: Asthma in preschool children: prevalence and risk factors.
Thorax 56:589-595, 2001. ♦♦

Response to Montelukast in Asthma Patients with Nasal Polyposis

MANY patients with intrinsic asthma--particularly those with aspirin sensitivity--will develop nasal polyps. Treatment for nasal polyposis may include intranasal corticosteroids, systemic steroids, or surgery; however, the recurrence rate is high. This study examined the effects of the leukotriene receptor antagonist montelukast when added to intranasal and inhaled corticosteroids for nasal polyps associated with asthma.

The study included 41 adult asthma patients with nasal polyposis that had failed to respond to long-term intranasal corticosteroid therapy. Twenty-four patients were classified as aspirin-sensitive, based on lysine aspirin intranasal challenge; the remaining 17 were considered aspirin-tolerant. While continuing intranasal and inhaled corticosteroid therapy, all patients received a 3-month trial of "add-on" montelukast, 10 mg/d.

Clinical improvement in nasal polyposis occurred with montelukast therapy in 64% of aspirin-tolerant and 50% of aspirin-sensitive patients. The change in clinical polyp score was significant only for the aspirin-tolerant group. Rates of subjective improvement in asthma were 87% and 61%, respectively. Changes in asthma score were significantly correlated with changes in polyp score. Aspirin-sensitive patients were more likely to have marked improvement in both clinical outcomes, whereas aspirin-tolerant patients generally had only mild to moderate improvement.

Only aspirin-tolerant patients had significant improvement in peak flow measurements. Neither group had significant changes in the results of acoustic rhinometry, nor in nasal inspiratory peak flow or nitric oxide level.

Though not placebo-controlled, this trial suggests that some patients with nasal polyposis and asthma respond to add-on therapy with montelukast. Aspirin-tolerant patients have a higher response rate than aspirin-sensitive patients, but patients in the latter group are more likely to have marked responses. No predictor of response to montelukast is identified; the variability of response may reflect heterogeneity of the leukotriene receptor.

COMMENT: *In this study, the addition of montelukast to treatment with an intranasal corticosteroid appeared to benefit the majority of patients with nasal polyps. The study was prospective but not placebo controlled. Although more aspirin-tolerant patients experienced benefit than aspirin-sensitive patients, those with aspirin sensitivity were more likely to experience marked improvement. As the authors point out, this suggests that in aspirin-sensitive patients with* ➤➤

nasal polyps, montelukast either works very well or not at all--ie, only a proportion of patients are responders.
J. R. B.
Ragab S, Parikh A, Darby YC, Scadding GK: An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma.
Clin Exp Allergy 31:1385-1391, 2001. ♦♦

Persistent Airflow Limitation in Severe Asthma Linked to Sputum Eosinophilia

SOME patients with asthma will develop persistent airflow limitation, despite being nonsmokers and receiving optimal therapy. Persistent airways obstruction has been linked to more severe asthma and to increased mortality, although its exact prevalence and risk factors remain uncertain. A group of patients with severe asthma were studied to determine the prevalence of persistent airflow limitation and the factors associated with this condition.

The study included 132 nonsmoking adult patients with severe asthma. All patients had been receiving inhaled corticosteroids and long-acting bronchodilators, yet continued symptomatic with at least one severe exacerbation during the past year. Pulmonary function tests were performed to assess the presence of persistent airflow limitation, while information on possible associated factors was gathered by questionnaire. Other assessments included airway response to histamine, tests of atopy, and induced sputum examination.

The prevalence of persistent airflow limitation was 48.5%. Patients in this group tended to be older and had a longer duration of asthma. There was no difference in asthma control, as judged by exercise tolerance, nocturnal symptoms, or use of rescue medications; patients with persistent airflow limitation had fewer exacerbations during the previous year.

The proportion of patients with a PC_{20} histamine of 1.0 mg/mL or lower was 67% among those with persistent airflow limitation, compared with 33% of those without this finding. Persistent airflow limitation was also associated with a higher rate of sputum eosinophilia, 69% vs 26%; and increased total IgE, 58% vs 41%. Patients with adult-onset asthma were more than three times likely to have persistent airways obstruction. However, on multiple logistic regression analysis, the only independent factor was sputum eosinophilia.

Among adult nonsmokers with severe asthma, the prevalence of persistent airflow limitation is about 50%. This condition is associated with adult-onset asthma and with airway hyperresponsiveness, but the most important risk factor is sputum eosinophilia. In these patients, uncontrolled inflammation appears to lead to structural airway changes and then to persistent airflow limitation.

COMMENT: *Persistent airflow obstruction, possibly by airway structural changes, was found to be common and related to airway hyperresponsiveness, sputum eosinophilia, and adult-onset disease. The high proportion of patients with incomplete reversibility of airflow obstruction was probably related to the severity of disease in these patients. All patients required at least a short course of systemic corticosteroids despite regular use of inhaled corticosteroids and long-acting bronchodilators. The strong association with eosinophilia strengthens the case for inflammation as the underlying cause of airway remodeling. Of note is that patients with and without persistent airway obstruction had comparable levels of asthma control as measured by exercise tolerance, nocturnal symptoms, and use of rescue medication.*
J. R. B.
ten Brinke A, Zwinderman AH, Sterk PJ, et al: Factors associated with persistent airflow limitation in severe asthma.
Am J Respir Crit Care Med 164:744-748, 2001. ♦♦

Airborne *Alternaria* Levels Linked to Airway Hyperresponsiveness in Children

ALTERNARIA is a very common fungus of known allergenicity--sensitization to *Alternaria* is associated with a 3-fold increase in asthma risk. However, there are few data on the respiratory effects of environmental exposure to *Alternaria* spores in children. This study examined the effects of *Alternaria* exposure and sensitization on airway symptoms and responsiveness in allergic children.

The study included 399 Australian schoolchildren with positive skin test results to at least 1 of 8 aeroallergens, including *Alternaria*, rye grass pollen, *Cladosporidium*, dust mite, and cat. A random sample of 220 children with positive skin test results to allergens other than *Alternaria* was selected as well. The children were studied on five occasions over a 3-year period, including assessment of histamine responsiveness, wheezing, and bronchodilator use. Daily airborne concentration of *Alternaria* spores was monitored throughout the study period.

Mean daily airborne *Alternaria* spore concentrations in ambient air over 1 month ranged from 2.2 to 307.7 spores/m^3. *Alternaria* concentrations were highest in the summer months and lowest during the winter. Increased *Alternaria* spore concentrations were associated with significant increases in airway responsiveness, wheezing, and bronchodilator use. The increase in airway responsiveness was heightened among children sensitized to *Alternaria* than other groups. Concentrations of grass pollen and *Alternaria* spores were strongly correlated with each other.

Environmental exposure to airborne *Alternaria* spores is associated with increased airway hyperresponsiveness among allergic children, particularly those sensitized to this common fungus. In areas of high *Alternaria* exposure, this may be an important contributor to severe asthma. However, it is difficult to separate out the effects of *Alternaria* from those of other airborne allergens.

COMMENT: Alternaria *is a common outdoor fungus and a significant allergen. This prospective study of 399 schoolchildren found an association between respi-* ➤➤

ratory symptoms, airway responsiveness, and airborne concentrations of Alternaria. *The association was much stronger in children sensitized to* Alternaria. *Though the findings are interesting, it is possible that exposure to other allergens or environmental pollutants could explain some of the observed effects.*
J.B.-M. Downs SH, Mitakakis TZ, Marks GB, et al: Clinical importance of Alternaria *exposure in children.*
Am J Respir Crit Care Med 164:455-459, 2001. ♦♦

Effects of Cromolyn Sodium in Aspirin-intolerant Asthma

ASPIRIN-intolerant asthma (AIA) is a common condition of uncertain pathogenesis. Past studies have established the value of cromolyn sodium in the treatment of AIA, though the mechanism of its effect is unclear. The effects of cromolyn sodium in patients with AIA were evaluated, including its impact on eosinophilic inflammation.

Sixteen adult patients with mild or moderate AIA were randomized to receive 1 week of treatment with cromolyn sodium, 20 mg/2 mL (1 ampule); or placebo four times daily. After a 2-week washout period, the patients were crossed over to the other treatment. In both conditions, patients underwent provocation testing with the cyclo-oxygenase inhibitor sulpyrine.

Treatment with cromolyn sodium significantly reduced symptoms, including nocturnal cough, wheezing, and asthmatic attacks. Cromolyn sodium was also associated with reduced bronchial responsiveness to sulpyrine, though there was no change in forced vital capacity or FEV_1. Cromolyn sodium also reduced blood and sputum eosinophilia, as well as sputum eosinophil cationic protein level.

In patients with AIA, treatment with cromolyn sodium reduces symptoms and airway responsiveness to sulpyrine. By suppressing eosinophilic infiltration and the secretory activity of eosinophils, cromolyn sodium may have a significant effect on the underlying inflammation associated with AIA.

COMMENT: *This well-designed placebo-controlled study reminds us that cromolyn has the potential to affect the immune response in asthma at multiple levels. Despite the availability of newer, more potent medications, cromolyn may offer benefit to some patients.*
A. M.
Amayasu H, Nakabayashi M , Akahori K, et al: Cromolyn sodium suppresses eosinophilic inflammation in patients with aspirin-intolerant asthma.
Ann Allergy Asthma Immunol 87:146-150, 2001. ♦♦

What's New in Food Allergy?

Chickpea: a Major Cause of Food Allergy in India

PATTERNS of food allergy in various countries depend on the foods commonly eaten in that region. In India, most people follow a vegetarian diet including large amounts of legumes, such as lentils, peas, and especially chickpeas. Chickpea hypersensitivity was assessed in a large series of Indian allergy patients, including in vivo and in vitro diagnostic findings and identification of major allergens.

The study included a random sample of 1,400 patients seen at three allergy clinics in Mumbai, India. Diagnosis included clinical history, skin prick testing, and double-blind placebo-controlled food challenges. Sodium dodecyl sulfate polyacrylamide gel electrophoresis and immunoblotting were performed to identify major chickpea allergens.

On screening, 4.2% of allergy patients had a positive history of chickpea allergy, with mainly respiratory symptoms. Skin testing was positive to chickpea in 69.5% of this group; four controls also had mildly positive reactions to chickpea. More than half (23/41) of the skin-test positive patients also had detectable IgE antibodies, and all patients in this group had a positive response to food challenge. The major chickpea allergens were proteins of 70, 64, 35, and 26 kD.

Particularly in India, chickpea can be an important cause of food allergy. Chickpea may cause potentially severe IgE-mediated hypersensitivity reactions. Efforts to purify chickpea allergen are underway.

COMMENT: *This report serves as an important reminder to allergists around the world that the ubiquitous chickpea--whether ingested in India or in a fashionable New York bistro--can be an important cause of anaphylaxis.*
A. M.
Patil SP, Niphadkar PV, Bapat MM: Chickpea: a major food allergen in the Indian subcontinent and its clinical and immunochemical correlation.
Ann Allergy Asthma Immunol 87:140-145, 2001. ♦♦

Allergen in Beer Identified as Lipid Transfer Protein

LIPID transfer proteins (LTPs) are small, highly conserved proteins found in a wide array of fruits and vegetables. They are the major allergen in Rosaceae fruits, but patients sensitized to LTPs may also react to many unrelated plant-derived foods, including nuts, legumes, and cereals. Allergy to beer is uncommon. This study identifies an LTP as an allergen in beer causing cross-reactivity in a patient with multiple food allergies. ➤➤

The patient was a 19-year-old man who had had severe episodes of urticaria and angioedema after drinking some brands of beer. He also reported an oral allergy syndrome after eating peaches. Skin prick testing showed strong reactivity to many different food allergens, including Prunoideae fruits, legumes, nuts, and cereals. Because no extract was available, skin testing to beer could not be performed.

Serologic studies revealed strong IgE reactivity to LTP purified from peach peel, as well as to a 10 kD protein found on apple and peach immunoblots. There was no evidence of IgE reactivity to birch cross-reactive allergens. Beer immunoblotting was negative, perhaps reflecting a low specific IgE level or a low allergen concentration in the beer extract used.

This patient's allergic reactions to beer appear to reflect hypersensitivity to a 10 kD LTP. This allergen, derived from barley, may cause cross-reactivity with LTPs in many other types of plant-derived foods. The LTP allergen appears to be heat- and enzyme-resistant and stable over long periods of time.

COMMENT: *The number of cross-reacting allergens among a variety of foods and airborne allergens continues to increase. These include profilin, chitinases, lipocalins, inhibitors of α-amylase, latex allergens, and LTPs. The presence of selected cross-reacting allergens in fruits, vegetables, and grains and the limited concentrations of many of these allergens in commercial food extracts may explain the inability to diagnose apparent ingestant reactions. Prick tests with fresh fruits and vegetables and peeling extracts may enhance recognition of sensitivity to some of these allergens.*
D. K. L.
Asero R, Mistrello G, Roncarolo D, et al: A case of allergy to beer showing cross-reactivity between lipid transfer proteins.
Ann Allergy Asthma Immunol 87:65-67, 2001. ♦♦

Chicken Serum Allergen Causes Cross-Reactivity in Bird-Egg Syndrome

THE cross-reactivity observed in patients with bird-egg syndrome--who have type I hypersensitivity to bird antigen as well as food allergy to egg yolk--has been ascribed to the allergen chicken serum albumin (CSA). However, challenge tests and environmental sampling studies to confirm the clinical relevance of CSA sensitization have not been performed. This study assessed the role of sensitization to CSA among patients with bird-egg syndrome.

Eight patients with respiratory symptoms caused by exposure to bird feathers and allergy symptoms after eating egg yolk were studied. In 6 of the patients, the respiratory symptoms included asthmatic reactions. Skin and serologic tests were performed to confirm sensitization to egg yolk and bird antigens. Bronchial, conjunctival, and oral CSA provocation tests were performed as well.

In each patient, skin tests were positive to egg yolk; chicken serum, meat, and feathers; and CSA. The patients also had specific IgE to the same allergens. Air sampling and immunoblotting revealed airborne CSA in one home with pet budgerigars. Bronchial challenge with CSA produced early asthmatic reactions in all of the asthma patients. Heating significantly reduced, but did not eliminate, the allergenicity of CSA.

The findings confirm that CSA can behave as both an inhalant and food allergen in patients with bird-egg syndrome. The allergen is heat-labile, which may explain why some patients sensitized to CSA can consume cooked but not raw eggs. It is recoverable as an airborne allergen and can cause asthmatic reactions on bronchial provocation.

COMMENT: *This article demonstrates the relationship of respiratory allergy and food allergy symptoms to a single allergen (ie, CSA) in the induction of the bird-egg syndrome. Chicken serum albumin is a cross-reactive allergen present in many avian pet species, such as budgerigar, parrot, pigeon, canary, and hen.*
E. J. B.
Quirce S, Marañón F, Umpiérrez A, et al: Chicken serum albumin (Gal d 5) is a partially heat-labile inhalant and food allergen implicated in the bird-egg syndrome. Allergy 56:754-761, 2001. ♦♦

Cilomilast Is Effective and Well-Tolerated in COPD

CHRONIC obstructive pulmonary disease (COPD) is a growing health problem with few treatments that affect the course of disease progression. With the recognized importance of inflammation in COPD, the use of inhaled corticosteroids has increased in recent years. The enzyme phosphodiesterase type 4 plays a key role in the metabolism of cyclic AMP, which
has important effects on bronchial smooth muscle tone and pulmonary inflammation. The selective phosphodiesterase-4 inhibitor cilomilast was evaluated for safety and efficacy in patients with COPD.

The multicenter, randomized, dose-ranging trial included 424 patients with COPD, mean FEV_1 46.8% of predicted. Those with primary asthma or poorly controlled COPD were excluded. Patients were randomized to receive 6 weeks of treatment with oral cilomilast at a twice-daily dose of 5, 10, or 15 mg or placebo. Trough FEV_1 before and after bronchodilator use was the main outcome of interest.

Pre- and postbronchodilator FEV_1 significantly improved in the cilomilast groups, compared with the placebo group. The cilomilast 15 mg group achieved a mean 130 mL increase in FEV_1, compared with a 30 mL decrease with placebo. Cilomilast also brought significant improvements in forced vital capacity and peak expiratory flow. Quality-of- life measures were somewhat improved with cilomilast, but the differences were not significant. Nausea was the most common adverse event, occurring most frequently in patients taking the higher doses of cilomilast. Few patients experienced vomiting.

Cilomilast 15 mg twice daily significantly improves expiratory flow in patients with moderate to severe COPD. This phosphodiesterase-4 inhibitor ➤➤

is well tolerated and offers bronchodilator, anti-inflammatory, and neuromodulatory effects. Cilomilast warrants investigation as maintenance therapy for patients with COPD.

COMMENT: *Cilomilast is an orally active, potent, selective phosphodiesterase type 4 inhibitor that is both a bronchodilator and anti-inflammatory agent with potential utility in all airway disorders. It is reasonably well tolerated, with nausea as the most common adverse event. In this study of 424 patients with chronic obstructive pulmonary disease (COPD), cilomilast 15 mg twice daily significantly improved FEV_1 compared with placebo. However, quality-of-life measures did not differ significantly. Further studies will be needed to determine whether this drug will have a place in the treatment of both COPD and asthma.*
E. J. B.

Compton CH, Gubb J, Nieman R, et al: Cilomilast, a selective phosphodiesterase-4 inhibitor for treatment of patients with chronic obstructive pulmonary disease: a randomised, dose-ranging study.
Lancet 358:265-270, 2001. ♦♦

REVIEWS OF NOTE

Liccardi G, Custovic A, Cazzola M, et al: Avoidance of allergens and air pollutants in respiratory allergy.
Allergy 56:705-722, 2001.

COMMENT: *This is a comprehensive review of a large body of clinical and experimental evidence suggesting that the increasing prevalence of allergic diseases--especially bronchial asthma--may be caused by changes of indoor/outdoor environments.*
E. J. B.

Kazatchkine ME, Kaveri SV: Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin.
N Engl J Med 345:747-755, 2001.

COMMENT: *In its "Advances in Immunology" series, the* New England Journal of Medicine *continues to publish remarkably succinct review articles on immensely complex topics in immunology. This one on intravenous immune globulin therapy points out that pooled intravenous immune globulin presumably contains the entire array of antigen-binding activities, including autoreactive natural antibodies that support immune homeostasis in healthy people, including cell growth, cytokine regulation, and lymphocyte differentiation. Therapeutic uses and safety concerns are discussed.*
R. J. M.

Leong KP, Huston DP: Understanding the pathogenesis of allergic asthma using mouse models.
Ann Allergy Asthma Immunol 87:96-109, 2001.

COMMENT: *This review details the importance of the mouse model of bronchial hyperresponsiveness in our current and future understanding of asthma*
AM.

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