ALLERGYWATCH®

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

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Inhaled Steroid Use Reduces Bone Mineral Density in Asthma Patients

MANY asthma patients use inhaled corticosteroids, often at daily doses of 800 µg or more. Studies of the possible adverse effects of inhaled corticosteroids on bone have yielded inconsistent results. The dose-response relationship between inhaled corticosteroid use and bone mineral density was analyzed in 196 adult patients with asthma. To reduce confounding by age and menopause, only patients 20 to 40 years of age were studied. All had used inhaled corticosteroids regularly for at least 6 months, but had only minimal exposure to systemic corticosteroids. Cumulative inhaled corticosteroid dose was estimated from questionnaire responses and medical records. Demographics, smoking, drug use, lung function, physical activity, and other factors were assessed as well. The effects of cumulative inhaled steroid dose on bone mineral density—measured at the lumbar spine and proximal femur—were assessed by multiple regression analysis.

The patients had been receiving inhaled corticosteroids for a median of 6 years, with a median cumulative dose of 876 mg. Eighty percent of patients were taking beclomethasone. The higher the cumulative inhaled corticosteroid dose, the lower the bone mineral density values at the lumbar spine, femoral neck, Ward's triangle, and trochanter. The inverse, linear relationship was significant before and after adjustment for age and sex. The effect was such that a doubling of inhaled corticosteroid dose carried a 0.16 (95% confidence interval, 0.04 to 0.28) SD reduction in bone mineral density at the lumbar spine.

Asthma patients using inhaled corticosteroids show significant reductions in bone mineral density at the lumbar spine and proximal femur. Over the years, the reductions in bone mineral density may have clinically significant effects on fracture risk. Different inhaled corticosteroids may have varying effects on bone mineral density.

COMMENT: *This was a large, cross-sectional study of the dose-response relation between cumulative* ➤➤

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

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- 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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inhaled corticosteroid dose and bone mineral density at the lumbar spine. It included 196 adults (119 women) with asthma, aged 20 to 40 years. Median duration of inhaled steroid treatment was 6 years (range 0.5 to 24.0) and median cumulative dose was 876 mg (87 to 4,380 mg). Study patients had received little or no oral, nasal, or parenteral steroid in the past. There was a definite negative association between cumulative dose and bone-mineral density. The size of the effect indicated that the bone mineral density of a patient who had taken 2,000 μg of an inhaled steroid daily for 7 years (5,110 mg) would be 1 standard deviation lower than that of a patient who had taken 200 μg daily for 1 year. This study should alert any clinician treating patients with chronic inhaled corticosteroids to monitor bone densitometry and prophylactically treat with calcium supplements.
E. J. B.
Wong CA, Walsh LJ, Smith CJP, et al: Inhaled corticosteroid use and bone-mineral density in patients with asthma. **Lancet** 355:1399-1403, 2000. ♦♦

Inhaled Salbutamol Use Does Not Increase Asthma Exacerbation Rate

SOME reports have suggested that regular use of inhaled β_2-agonists, especially at high doses, can increase morbidity and mortality from asthma. This has led to recommendations that these medications be used only when necessary for symptom relief, and that inhaled corticosteroids be added when inhaled β_2-agonists must be used more than once daily. The Regular Use of Salbutamol Trial (TRUST) sought to clarify the effects of long-term inhaled salbutamol use on asthma control.

The study included 983 adult asthma patients receiving at least twice-weekly therapy with a short-acting β_2-agonist. Ninety percent were also taking inhaled corticosteroids, at a dose no higher than 2 mg/d. The patients were randomly assigned to receive salbutamol, 400 μg via Diskhaler 4 times daily, or placebo; treatment continued for 1 year. The groups were stratified according to inhaled corticosteroid use and dosage. They were compared for asthma exacerbation rate, assessed from daily diary cards, and for secondary outcomes.

The two groups were similar in all characteristics, including sex, age, smoking, inhaled corticosteroid use, asthma severity, and bronchodilator use. There were no significant differences in the annual asthma exacerbation rate; the timing and duration of exacerbations were similar as well. There were no serious adverse events; the rate of minor adverse events was 8% with salbutamol and 5% with placebo.

Long-term use of inhaled salbutamol does not appear to increase the rate of asthma exacerbations, even in patients receiving inhaled corticosteroids as well. The findings question guidelines placing significant restrictions on the use of inhaled β_2-agonists. However, patients who require increasing doses of inhaled β_2-agonists do not have optimal asthma control, and should therefore be considered for additional treatment.

COMMENT: *Previous reports suggested that long-term regular use of inhaled β-agonists resulted in a deterioration in asthma control. This randomized, double-blind, placebo-controlled trial in 983 patients, 90% of whom were taking inhaled corticosteroids, revealed no evidence that regular use of inhaled salbutamol, 400 μg 4 times daily for 1 year, increased the exacerbation rate of asthma. The authors emphasize that the need for increased doses of inhaled β-agonists is an indication of suboptimal asthma control. Additional therapy should be considered in this situation.*
E. J. B.
Dennis SM, Sharp SJ, Vickers MR, et al: Regular inhaled salbutamol and asthma control: the TRUST randomised trial.
Lancet 355:1675-1679, 2000. ♦♦

Intranasal Budesonide Has Short Onset of Action Against Rhinitis Symptoms

ALTHOUGH intranasal steroids are the most effective treatment for allergic rhinitis, they do not reach peak efficacy until a few days after the start of treatment. In contrast, oral antihistamines show evidence of efficacy within 5 to 7 hours. Budesonide is available in a new aqueous suspension (Rhinocort Aqua), with concentrations of 0.64 and 1.28 ng/mL providing a total daily dose of 64 to 256 µg. The time to onset of action of budesonide aqueous nasal spray (BANS) was assessed, including a comparison of the two strengths.

The randomized, double-blind trial included 217 patients with ragweed pollen-induced seasonal allergic rhinitis. The subjects were exposed to ragweed pollen in an environmental exposure unit for 14 hours and randomized to receive BANS, 64 or 256 µg, or placebo. The patients were offered measures to prevent or relieve allergic eye symptoms; no other treatments were given. The treatments were compared for their effect on nasal symptoms, individually and in a combined nasal score; patient ratings of efficacy; and peak nasal inspiratory flow.

Patients treated with BANS showed a sustained onset of action at 7 hours after treatment. At the 64 µg dose, time to onset of action was 5 hours overall, and 3 hours for the symptom of runny nose. A significant effect on peak nasal inspiratory flow was evident at 3 hours. From 7 to 12 hours, BANS was more effective than placebo in reducing combined nasal symptoms and the symptom of blocked nose.

In patients with seasonal allergic rhinitis, BANS relieves nasal symptoms within 7 hours after administration. Some symptoms may be relieved within 3 hours. Patient reports suggest that the 64 µg dose performs just as well as the 256 µg dose.

COMMENT: *Rapid onset of action for medications in treating allergic rhinitis is paramount, as many patients do not start medications before developing symptoms. Antihistamines have been shown in numerous studies to lead to symptom relief in just 3 to 5 hours, whereas intranasal corticosteroids take hours to days. This study, using a pollen chamber, showed that intranasal aqueous budesonide improved combined nasal symptom scores within 7 hours, with the first improvement seen at 3 hours. This study could change our thinking about intranasal corticosteroids. These agents can provide a quick onset of action, much like antihistamines, in controlling allergic nasal symptoms.*
M. S. B.

Day JH, Briscoe MP, Rafeiro E, et al: Onset of action of intranasal budesonide (Rhinocort Aqua) in seasonal allergic rhinitis studied in a controlled exposure model. **J Allergy Clin Immunol** 105:489-494, 2000. ♦♦

Critique Reveals Flaws in Published Reviews of Asthma Treatment

OPTIONS for asthma treatment are expanding rapidly, making it difficult to determine the most appropriate treatment for a given patient. Systematic reviews and meta-analyses are commonly published to help physicians deal with this "information overload." However, many reviews have methodologic flaws that reduce their value. The methodologic characteristics of reviews of asthma treatment were evaluated, including an evaluation of reviews published by the Cochrane Collaboration.

The investigators identified 50 systematic reviews or meta-analyses of asthma treatment. Fifty-eight percent of the reviews were published in 1997 and 1998. Twelve were published in the *Cochrane Library* and 38 in peer-reviewed journals. The journal with the most published reviews was *Annals of Pharmacotherapy*, followed by *Journal of Allergy and Clinical Immunology* and *Respiratory Medicine*. Most of the reports addressed the use of steroids or β agonists; only 2 addressed immunotherapy.

Analysis of methodologic quality revealed serious or extensive shortcomings in 40 of the 50 papers. This included all 6 reviews funded by industry. Overall quality was better for reviews published in the *Cochrane Library*. Key findings of reviews with minimal design flaws included the efficacy of allergen-specific immunotherapy on symptoms and drug requirements, despite the lack of effect on lung function; the inefficacy of measures to reduce mite exposure at home; the lack of indication for methotrexate in patients receiving long-term oral steroids; and the benefits of short-course oral corticosteroids for acute asthma exacerbations.

Most systematic reviews and meta-analyses of asthma treatment are of poor methodologic quality. Reviews published by the Cochrane Collaboration tend to be of higher quality. Peer-reviewed journals should make similar efforts to ensure the quality of the reviews they publish.

COMMENT: *Physicians are bombarded on a regular basis with journal articles reviewing the medical management of asthma. Critical analysis of articles is paramount in determining proper pharmacologic treatment for the patient. Jadad et al evaluated published systemic reviews and meta-analyses in the treatment of asthma over the last several decades. Their findings of highly flawed methodology in many of these articles found in peer-reviewed journals should caution the physician to have a more jaundiced eye in evaluating the literature on asthma management.*
M. S. B.

Jadad AR, Moher M, Browman GP, et al: Systematic reviews and meta-analyses on treatment of asthma: critical evaluation. **BMJ** 320:537-540, 2000. ♦♦

Loratadine and Fexofenadine Have Lowest Incidence of Sedation

THE major advantage of the second-generation antihistamines is their reduced rate of side effects, particularly sedation. The sedative effects of 4 of these agents—loratidine, fexofenadine, cetirizine, and acrivastine—were compared using postmarketing surveillance data. The study was based on the British prescription-event monitoring system, in which routine questionnaires are sent to general practitioners to inquire about adverse affects potentially related to a prescription drug. Data on 46,363 patients receiving second-generation antihistamines were analyzed to determine the incidence of sedation or drowsiness for each drug. Data were collected for several months after each drug was released to market.

All 4 drugs had a low incidence of sedation. Sedation was least frequent with loratadine and fexofenadine. Adjusted odds ratios suggested a 3.5-fold increase in the incidence of sedation with cetirizine and a 2.8-fold increase with acrivastine, compared with loratadine. None of the drugs was associated with any increase in accident or injury risk.

Second-generation antihistamines all have a low incidence of sedation. This risk is particularly low for loratadine and fexofenadine; therefore these drugs may be preferred when safety is a critical concern.

COMMENT: *The side effects of a new medication may not be appreciated and the true incidence of a side effect known in the population until the agent has been used by thousands of patients. This British study used physician-prescribing event monitoring to evaluate the degree of sedation associated with 4 second-generation antihistamines. Only 1 out of 140 patients complained of sedation with the newer antihistamines, though loratadine and fexofenadine clearly had significantly lower sedation the cetirizine and acrivastine. These "real world" data confirm the difference in sedation between these 4 agents documented in previous clinical trials. This information is important if patients being prescribed a newer antihistamine could be affected at work or play by possible drowsiness.*
M. S. B.
Mann RD, Pearce GL, Dunn N, Shakir S: Sedation with "non-sedating" antihistamines: four prescription-event monitoring studies in general practice.
BMJ 320:1184-1187, 2000. ♦♦

Allergies Cause Cognitive Deficits in Some Patients

PATIENTS with allergies commonly complain of central nervous system symptoms, such as concentration difficulties, slowed thinking, and poor memory. Although antihistamines are known to affect cognitive function, few studies have sought to determine whether the allergic reaction itself may have cognitive effects. The few studies of this issue preselected allergic patients with depressive symptoms.

Detailed cognitive testing was performed in patients with a history of seasonal allergic symptoms with a positive skin prick test to ragweed. The patients were not selected according to symptoms of mood, fatigue, or cognitive difficulties. They were not taking antihistamines or other drugs that could affect test performance. Cognitive tests—including the Buschke Selective Reminding Test, Sternberg memory scanning task, Digit Span Forward and Backward, Hick paradigm choice reaction time, Salthouse Listening Span Task, Conners Continuous Performance Test, and Paced Auditory Serial Addition Test—were performed in and out of ragweed season. Cognitive performance was compared with that of nonallergic controls.

Before the study, 53% of the allergy patients reported problems paying attention during allergic reactions, 47% had slowed thinking, and 44% had memory problems. Cognitive tests showed subtle reductions in cognitive processing speed in allergic patients during ragweed season. Performance on tests of attention and recent memory was not significantly reduced, although some patients had reductions in working memory.

During allergic reactions, some patients with seasonal allergic rhinitis have subtle slowing of cognitive processing speed and/or problems with working memory. However, the study does not confirm the common patient complaints of attention and memory problems. Further studies of the cognitive effects of allergy are needed, perhaps limited to patients who complain of cognitive difficulties or those with severe allergy.

COMMENT: *Most allergists would readily recognize that seasonal allergic rhinitis affects the performance of their patients at many levels. Previous studies have focused on the effects of potential CNS impairment of anti-allergic drugs. In this interesting study the authors note that symptomatic adult patients with ragweed rhinitis without CNS-active pharmacotherapy have measurable impairment in cognitive function. It is likely that these effects are further potentiated by the effects of sedating antihistamines.*
A. M.
Marshall PS, O'Hara C, Steinberg P: Effects of seasonal allergic rhinitis on selected cognitive abilities.
Ann Allergy Asthma Immunol 84:403-410, 2000. ♦♦

Long-Term Follow-Up Study Tracks Course of Asthma Through Adulthood

LONG-term follow-up studies provide essential insights into the prognosis of asthma. This study followed up a cohort of college freshman for 23 years to determine the prevalence of asthma over time and the outcomes of asthma symptoms. A total of 1,601 subjects were interviewed regarding symptoms of asthma and allergic rhinitis. One thousand twenty-one subjects returned a follow-up questionnaire 23 years later, of whom 738 had undergone skin testing as freshmen. Mean age at follow-up was 40 years.

Eighty-four subjects had a history of asthma: 48 had had asthma as freshmen, and 36 had developed asthma subsequently. Of all patients with a history ➤➤

of asthma, 52% had active asthma and 48% were symptom free. Fifty percent of the patients with active asthma reported that their condition had improved and 39% said they had no change. Nine percent believed their asthma had gotten worse. A positive skin-test result did not predict asthma outcome at follow-up.

Long-term follow-up suggests that the cumulative prevalence of asthma continues to increase from college age through age 40 years. About 5% of all asthma patients report severe or worsening asthma during this time. Atopy does not predict the long-term outcome of asthma.

COMMENT: *This group of investigators has provided interesting insights concerning the natural history of allergy and asthma based upon a cohort of incoming freshmen at Brown University. This latest addition of follow-up information includes 1,021 subjects who returned their questionnaires 23 years after the original evaluation, with 738 of this population having been skin-tested to inhalant allergens. Positive skin tests to allergens in subjects with rhinitis are associated with the development of asthma (3-fold greater risk), but positive skin tests were not of prognostic value in predicting outcome of asthma during the 23-year follow-up. This article is a valuable addition to the long-term outcome literature of allergy and asthma.*
D. K. L.

Settipane GA, Greisner WA III, Settipane RJ: Natural history of asthma: a 23-year follow-up of college students. **Ann Allergy Asthma Immunol** 84:499-503, 2000. ♦♦

Tests for Penicillin-Induced Skin Reactions Examined

CUTANEOUS reactions to amoxicillin and penicillin G may be immediate or delayed; most are morbilliform or erythematous exanthema. Although few studies have addressed the pathogenesis of these reactions, a T-cell mediated process seems likely. The diagnostic use of skin and in vitro tests for penicillin G- and amoxicillin-induced morbilliform skin eruptions was examined in 12 patients. All patients met exclusive criteria for immediate or delayed-type skin reactions; 6 controls without hypersensitivity reactions were studied for comparison. "Scratch/patch" skin tests, consisting of a gentle 1 cm scratch, were performed using penicillin G and amoxicillin. The subjects also underwent measurement of specific IgE to penicillin and lymphocyte transformation tests (LTT).

Twelve of the patients had delayed-type reactions, but none had a clearly positive result for specific IgE and none had a positive immediate penicillin skin test. However, 9 of the 12 patients had a positive reaction to the scratch/patch test, compared with none of the patients with clinically immediate reactions and none of the controls. Thus this test had a negative predictive value of 67% and positive predictive value of 100%. The LTT was positive in 10 of 12 patients with delayed-type reactions. This test was also negative in patients with immediate reactions and in controls. It had a negative predictive value of 75% and positive predictive value of 100%.

Patients with delayed reactions to penicillin G or amoxicillin show no evidence of IgE-mediated sensitization. However, the scratch/patch test and LTT are positive in most patients. These findings suggest a role of drug-specific T cells in most delayed reactions to these drugs. The clinical significance of a positive patch or LTT remains uncertain.

COMMENT: *The majority of amoxicillin- and penicillin G-induced cutaneous reactions are delayed-onset morbilliform exanthema. The pathogenesis of these reactions is still uncertain, but the evidence presented in this and other studies points to T-cell mediated delayed-type hypersensitivity. The patch testing described here had a negative predictive value of 67% and a positive predictive value of 100%. This test can easily be done in most offices and might be useful in predicting the risk of re-exposure in patients with a history of penicillin allergy.*
J. R. B.

Schnyder B, Pichler WJ: Skin and laboratory tests in amoxicillin- and penicillin-induced morbilliform skin eruption. **Clin Exp Allergy** 30:590-595, 2000. ♦♦

Experimental Dermatitis Is Driven by Superantigen-Mediated T-Cell Activation

STAPHYLOCOCCUS aureus colonization is common in patients with atopic dermatitis (AD) and other inflammatory skin diseases. Most of these strains produce enterotoxins with superantigen properties. In a previous study, the investigators found that application of the superantigen staphylococcal enterotoxin B (SEB) causes eczema on either healthy or atopic skin. They studied the mechanism of this effect in 6 patients with untreated AD and 6 healthy controls. In each subject, areas of skin were treated with SEB, vehicle, and sodium lauryl sulfate, and then biopsied. The specimens were analyzed to determine whether the SEB-induced dermatitis represented a T cell-superantigen-mediated reaction or nonspecific cytokine-driven inflammation.

As in the previous study, SEB caused dermatitis in both AD patients and healthy controls. In both groups, the SEB-treated areas showed specific accumulation of T cells expressing SEB-reactive T-cell receptor Vβ 12 and 17. Sodium lauryl sulfate application did not produce the same selective T-cell upregulation.

The skin inflammation caused by SEB application is associated with significant and selective accumulation of T cells expressing SEB-reactive T-cell receptor Vβ 12 and 17. The implications for clinical AD are unknown, but staphylococcal superantigens may play a role in exacerbation of AD after colonization with *S. aureus*. Future studies should include direct staining for superantigens in the skin, with demonstration of T cells specific for that superantigen.

COMMENT: *Atopic dermatitis can be caused or aggravated by SEB, but the mechanism is not* ➤➤

obvious. These authors found that SEB acts as a superantigen that induces T cell activation, not only in AD patients but even in healthy subjects. If you are tempted to ask whether AD is an allergic or an infectious disease, the answer may well be "yes."
R. J. M.
Skov L, Olsen JV, Giomo R, et al: Application of staphylococcal enterotoxin B on normal and atopic skin induces up-regulation of T cells by a superantigen-mediated mechanism.
J Allergy Clin Immunol 105:820-826, 2000. ♦♦

Does Acetaminophen Use Contribute to Asthma?

THE antioxidant glutathione (GSH) plays a key role in preventing oxidative damage to the lung. In animal models, treatment with paracetamol depletes the lung of GSH. If the same effect occurs in humans, it could reduce pulmonary defenses against oxidative stress, potentially leading to increased asthma morbidity. Population-based data were used to assess the association between paracetamol use and asthma.

As part of a larger case-control study of dietary antioxidants and asthma, the analysis included 664 patients with asthma and 910 without. All subjects were 16 to 49 years of age. The definition of asthma was based on screening questions regarding asthma attacks and antiasthma medications; asthma severity was assessed by frequency of night wakings and impact on daily activities. As part of an extensive lifestyle questionnaire, subjects were asked how often they used paracetamol and aspirin. The relationship of these drugs to asthma and asthma severity was assessed by logistic regression analysis.

Smoking status was unrelated to asthma. However, daily or weekly use of paracetamol was strongly associated with asthma, even after controlling for potential confounders. This relationship was observed in subjects who did and did not use aspirin. It was particularly strong among asthmatic subjects with more severe disease: asthma severity tended to increase with increasing paracetamol use. Paracetamol use was associated with rhinitis in nonasthmatic controls, but not in asthmatic cases.

Paracetamol use is strongly associated with asthma, even after controlling for possible confounding factors. No causal relationship can be assumed: it may be that patients take paracetamol to relieve their asthma symptoms, or to avoid potential sensitivity reactions to aspirin. There are many good reasons why paracetamol should remain the preferred analgesic medication. However, some patients may be able to reduce their frequency of paracetamol use.

COMMENT: *The pulmonary antioxidant GSH may limit airway inflammation in asthma, and paracetamol (acetaminophen) depletes lung GSH in animals. This study compared the frequency of use of paracetamol and aspirin in 664 individuals with asthma and 910 subjects without asthma. Paracetamol was positively associated with asthma. It was present in users and nonusers of aspirin, and stronger when cases with more severe disease were compared with controls. Contrary to popular belief, use of paracetamol may contribute to asthma and rhinitis morbidity in adults. Though not studied, there is every reason to believe this would be true in children as well. This study shows a strong association between acetaminophen and asthma; further studies will be required to demonstrate a cause-and-effect relationship.*
E. J. B.
Shaheen SO, Sterne HAC, Songhurst CE, Burney PGJ: Frequent paracetamol use and asthma in adults.
Thorax 55:266-270, 2000. ♦♦

Airway Eosinophilia Differentiates Asthmatic From Postinfectious Cough

CHILDREN often develop a persistent cough after a respiratory infection. About half of these coughs are associated with a positive methacholine challenge, and many are treated as asthma. Few studies have examined the pathophysiology of such postinfectious coughs, and how they differ from asthma. This study compared eosinophil counts in induced sputum between children with persistent postinfectious cough vs children with allergic asthma.

The study included 12 children with persistent cough (1 month or longer) after apparent respiratory tract infection. None of the children had received corticosteroids. Two groups of children with atopic asthma were studied as well: 11 treated with inhaled corticosteroids and 11 untreated. Induced sputum samples were obtained for measurement of eosinophil count. Peripheral blood eosinophils, serum eosinophil cationic protein (ECP), and nasal lavage eosinophils were measured as well.

Median percentage of eosinophils was 0.5% in children with apparent postinfectious cough vs 14.5% in those with untreated atopic asthma. The children with postinfectious cough also had a lower blood eosinophil count, serum ECP, and nasal lavage eosinophil percentage. There was no difference in sputum eosinophils between the children with postinfectious cough and asthmatic children receiving inhaled steroids.

Children with persistent, postinfectious cough do not show eosinophilic inflammation in induced sputum samples. This is despite the fact that some children with postinfectious cough have airway hyperreactivtiy. The findings have important implications for the recognition and treatment of postinfectious cough in children. This condition is pathophysiologically different from asthma, and may respond differently to inhaled steroids.

COMMENT: *Chronic cough is a frequent symptom in pediatrics, especially in children with asthma. It can be difficult to distinguish a postinfectious chronic cough from one caused by asthma. Zimmerman et al. clearly distinguish between the two by measuring airways eosinophilia by induced sputum. Methacholine challenge fails to separate the two types of cough. This study defines the two by differences in pathology, which* ➤➤

should lead to further research in appropriate medical management.
M. S. B.
Zimmerman B, Silverman FS, Tarlo SM, et al: Induced sputum: comparison of postinfectious cough with allergic asthma in children.
J Allergy Clin Immunol 105:495-499, 2000. ♦♦

High-Dose Methylprednisolone Potentiates Oral Anticoagulants

PREVIOUS studies of the effects of oral corticosteroids on the activity of oral anticoagulants have given conflicting results: some have shown increased anticoagulant effects, while other have shown decreased effects. The authors recently encountered a patient receiving oral anticoagulants who demonstrated a sharp rise in international normalized ratio (INR) when given methylprednisolone. They studied this potential interaction further in 10 consecutive patients receiving concomitant methylprednisolone and oral anticoagulants. All patients were taking vitamin K antagonists: 8 fluindione and 2 acenocoumarol. Indications for anticoagulant use included atrial fibrillation, antiphospholipid syndrome, and thromboembolism. Two patients were taking amiodarone at the same time, but the dose had not recently been modified.

Changes in clotting tests were evaluated during administration of pulse methylprednisolone. The patients' mean INR increased from 2.75 (range 2.02 to 3.81) at baseline to 8.094 (range 5.32 to 20.0) after intravenous methylprednisolone. A group of controls showed no increase in prothrombin time in response to methylprednisolone.

In patients taking oral anticoagulants, concomitant methylprednisolone administration may produce a sharp increase in INR. High-dose methylprednisolone appears to potentiate the effects of oral anticoagulants. These 2 types of medications are often given together in clinical practice; such patients should undergo daily monitoring to ensure adequate anticoagulation.

COMMENT: *In the course of caring for severe cases of allergic inflammation or hypersensitivity disorders, clinical allergists may occasionally be required to use high doses of methylprednisolone. Previous studies had shown both enhanced and diminished activity of oral anticoagulants when administered with oral corticosteroids. In this study, intravenous high-dose methylprednisolone significantly potentiated the action of oral anticoagulants. Since many patients require the use of oral anticoagulants on a chronic basis, this potential drug interaction is important to be aware of!*
A. M.
Costedoat-Chalumeau N, Amoura Z, Aymard G, et al: Potentiation of vitamin K antagonists by high-dose intravenous methylprednisolone.
Ann Intern Med 132:631-635, 2000. ♦♦

Losing Weight Improves Asthma Outcomes in Obese Patients

UP to 20% of the population is obese, including many patients with asthma. Obesity can lead to worsening of asthma in many ways. The effects of a weight-reduction program on lung functions and other outcomes were studied in obese patients with asthma. The study included 38 patients with previously diagnosed asthma and obesity, defined as a body mass index of 30 to 42 kg/m^2. All patients had a spontaneous diurnal variation in their asthma or at least a 15% response to bronchodilators; all were current nonsmokers. One half of the patients were randomized to a supervised weight-reduction program, including an 8-week very-low-energy diet. The effects of weight loss on various lung function measures were studied. Other outcomes included asthma symptoms, number of acute asthma episodes, need for oral steroids, and health status.

Patients in the weight-reduction group lost a mean of 14.2 kg, or 14.5% of their baseline weight. One-half of these patients lost at least 15% of their baseline body weight. Mean weight loss in the control group was only 0.3%. At 1 year, weight was still reduced by 11.3% in the weight-reduction group, compared with a gain of 2.2% in the control group. Forced expiratory volume in 1 second improved to a significantly greater extent in the weight-reduction group. At 1 year's follow-up, there was still a 7.6% difference in FEV_1. Weight loss was also associated with a significant reduction in dyspnea and a nonsignificant decrease in the use of rescue medications. Health status improved to a significantly greater extent in the weight-reduction group.

In obese asthma patients, weight loss can significantly improve lung function, asthma symptoms, and health status. This effect may result from a reduction in closing capacity and/or in gastrointestinal reflux. Although the patients' overall clinical status is improved after weight loss, airway hyperreactivity persists. The 12-week supervised weight-reduction program used in this study appears effective and economical.

COMMENT: *Several recent studies have documented that obesity worsens asthma. Until now, there have been no investigations into whether weight-management programs improve asthma outcomes. Stenius-Aarniala et al. demonstrate that a weight-reduction program does improve lung function parameters, leading to fewer exacerbations and reduced need for corticosteroid bursts. Weight management programs should be recommended for all obese patients with asthma.*
M. S. B.
Stenius-Aarniala B, Poussa T, Kvarnström J, et al: Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. **BMJ** 320:827-832, 2000. ♦♦

Is Chest Compression Alone the Choice for Bystander CPR?

BYSTANDER-initiated CPR significantly improves survival for patients with out-of-hospital car- ➤➤

diac arrest. However, even in Seattle—an area with extensive citizen training in CPR—about one-half of victims of witnessed out-of-hospital arrests do not receive bystander-initiated CPR. Experimental studies suggest that survival is similar with chest compressions alone as with chest compressions plus mouth-to-mouth ventilation. This issue was addressed in a randomized trial performed by the Seattle emergency medical services system. Bystanders at the scene of an apparent cardiac arrest were instructed to perform either chest compressions alone or chest compressions plus mouth-to-mouth ventilation. The study was designed to detect at least a 3.5% improvement in survival to hospital discharge with full CPR.

Of 1,296 randomized episodes, 776 were excluded for reasons such absence of cardiac arrest; cardiac arrest from specific causes, including drug overdose; and absence of advanced cardiac life support. This left 520 episodes: 241 assigned to chest compressions alone and 279 to chest compressions plus mouth-to-mouth ventilation. Bystanders in cases assigned to chest compression only were more likely to receive complete instructions, which took 1.4 minutes less to deliver than instructions for compression plus mouth-to-mouth ventilation. Survival to hospital discharge was 14.6% with chest compression alone and 10.4% with chest compression plus mouth-to-mouth ventilation.This difference was nonsignificant.

In witnessed, out-of-hospital cardiac arrest, chest compression alone offers outcomes similar to those of full CPR. For bystanders inexperienced in CPR, chest compressions alone may be the preferred technique. The study was performed in an emergency medical services system with short response times and a tightly structured dispatch protocol, and did not follow strict intention-to-treat analysis.

COMMENT: *Cardiopulmonary resuscitation methods usually include both cardiac compression and ventilation. I don't know about you, but there are times when the mouth-to-mouth ventilation part is difficult for me to contemplate (eg, facial trauma and bleeding, vomiting). Additionally, inexperienced people often have difficulty mastering the ventilation but not the cardiac compression. This Seattle study showed that inexperienced administrators of chest compression alone did at least as well (in saving the patient) as those attempting the combination.*

R. J. M.

Hallstrom A, Cobb L, Johnson E, Copass M: Cardiopulmonary resuscitation by chest compression alone or with mouth-to-mouth ventilation.

N Engl J Med 342:1546-1553, 2000. ♦♦

Comprehensive Intervention Improves Outcomes for Low-Income Children with Asthma

ASTHMA is a highly prevalent problem among low-income, minority children, with increased rates of emergency department (ED) utilization, hospitalization, and death. Although various types of outreach programs have been developed for children with asthma, there have been few controlled trials in low-income, minority populations. A comprehensive intervention program was evaluated in Medicaid-insured asthmatic children.

Eighty such patients, aged 2 to 16 years, were identified on the basis of frequent ED visits or hospitalizations for asthma. All children received usual clinical care. In addition, one group was randomized to receive an educational and outreach intervention, including care in a tertiary care pediatric allergy clinic. The intervention focused on providing care in accordance with National Heart, Lung, and Blood Institute guidelines. The patients were followed up for 1 year to assess ED visits, hospitalizations, and health care charges.

The 2 groups were similar in their demographic characteristics. Mean number of ED visits in the year before the study was 3.5, mean number of hospitalizations 0.6, and mean health care charges $2,969. During the year of the study, ED visits decreased to 1.7 in the intervention group vs 2.4 in the control group. Hospitalizations decreased to 0.2 vs 0.5, respectively. Health care charges were significantly lower in the intervention group as well.

The comprehensive intervention evaluated in this study—including education, medical management to meet current guidelines, and effective outreach—significantly improves outcomes in pediatric asthma patients on Medicaid. Reductions in health care utilization may yield cost savings, although formal cost-benefit analysis is needed. The study did not address the costs of outpatient medications.

COMMENT: *This randomized, controlled study was performed with families of asthmatic children who had been to the ED or hospital for asthma. Though a number of similar studies have been done in the past, this one included an appropriate control group, which most such studies have lacked. Studies without such a control group take advantage of a phenomenon called regression to the mean, which simply means that the sickest patients tend to get better over time on their own, without intervention. By documenting that the intervention—in this case, education and regular follow-up—reduced utilization in the intervention group and not the control group, the results are far more credible than in uncontrolled studies. A number of factors were not controlled for, including medication refills to document compliance, and many patients were not regularly accessible for follow-up evaluation. Still, the results add to the accumulating evidence that aggressive intervention is helpful in asthma, even among impoverished families with young children.*

J. M. P.

Kelly CS, Morrow AL, Shults J, et al: Outcomes evaluation of a comprehensive intervention program for asthmatic children enrolled in Medicaid.

Pediatrics 105:1029-1035, 2000. ♦♦

Studies Support Ethnic Component to Asthma Risk

THE effects of lifestyle vs race or ethnicity on the risk of developing asthma remain unclear. Two ➤➤

new studies provide additional insights into this question. One study analyzed the risk of atopic disorders in three groups of subjects living in Sweden: a group born in Turkey and a group born in Chile, along with their Swedish-born offspring; and a sample of Swedish-born parents and their children. The rate of allergic asthma was highest in the Chilean group—more than twice as high as in the Swedish-born group. In contrast, the Turkish group had the lowest rate of allergic rhinoconjunctivitis. All atopic disorders were less frequent in the Turkish group than in the Chilean group.

The other study assessed the effect of race on factors associated with asthma among middle-class children living in the suburbs of Detroit. The study included 569 children, aged 6 to 8 years; 14% were African-American. Forty-two percent of the African-American children reacted to methacholine, compared with 22% of European-American children. Geometric mean total IgE was 60.6 vs 27.7 IU/mL, respectively.

These studies support the concept that race or ethnicity significantly affects the risk of atopic disorders, independent of external childhood environment. Even though the children in both the Chilean and Turkish groups were born in Sweden, their rates of atopic disorders differed significantly. The finding of racial differences in total serum IgE and airway responsiveness among middle-class children in Detroit suggests that African-American children may be predisposed to asthma.

COMMENT: *When people from parts of the worlds with a low prevalence of asthma assume a "westernized" lifestyle, the prevalence of atopy and asthma rises. Within the United States, socioeconomic factors have been assumed to account for the higher asthma morbidity and mortality among African-American children. In contrast, these two studies add to the evidence that ethnic or racial differences influence the predisposition toward developing asthma, independent of environmental or socioeconomic factors.*
S. A. T.

Hjern A, Haglund B, Hedlin G: Ethnicity, childhood environment and atopic disorder. Clin Exp Allergy 30:521-528, 2000.
Joseph CLM, Ownby DR, Peterson EL, Johnson CC: Racial differences in physiologic parameters related to asthma among middle-class children.
Chest 17:1336-1344, 2000. ♦♦

Increased ECP Predicts Hyperresponsiveness in Sensitized Children

EOSINOPHILIC infiltration is found even in early asthma. Because activated eosinophils release eosinophil cationic protein (ECP), measurement of ECP in blood or tissue may provide useful information on the early development of asthma. The relationship between serum ECP level and later development of asthma or bronchial hyperresponsiveness was examined in 240 young subjects. When first studied by blood and skin prick tests at a mean age of 14 years, 147 subjects had no sensitization to allergens, group 1; 55 were sensitized, with a serum ECP level of less than 20 µg/L; 16 were sensitized, with a serum ECP level of 20 µg/L or higher; and 22 had physician-diagnosed asthma or methacholine hyperresponsiveness. A mean of 6 years later, the subjects underwent methacholine provocation testing.

Methacholine responsiveness was somewhat higher at follow-up: median PD_{15} increased from 11.7 to 20.5 µmol. At baseline, there was no significant difference in bronchial responsiveness between sensitized subjects with and without elevated ECP. However, at follow-up, responsiveness was significantly greater in the sensitized subjects with elevated ECP: median PD_{15} was 12.7 µmol in group 2 vs 20.5 µmol in group 3. In a logistic regression model using methacholine hyperresponsiveness as the dependent variable, the odds ratios were 2.2 (95% confidence interval 0.8 to 6.6) in group 2 vs 5.9 (95% confidence interval 1.6 to 21.7) in group 3, compared with group 1.

In adolescents who are sensitized to allergen but not yet asthmatic, an elevated serum ECP level predicts an increased rate of methacholine responsiveness at follow-up. The increased bronchial reactivity noted in this study is unexplained by an increase in allergy. Study limitations include the small size of the sensitized groups and the arbitrary cutoff point for elevated ECP.

COMMENT: *At age 14, the atopic subjects with elevated ECP levels did not differ from the other atopic subjects with respect to rhinitis, eczema, or skin test wheal diameter. By age 20, nearly one-third of these patients exhibited bronchial hyperresponsiveness. This suggests that among teens, serum ECP level may be a marker for the development of subsequent bronchial hyperresponsiveness.*
S. A. T.

Rasmussen F, Lambrechtsen J, Siersted HC, et al: Increased eosinophil cation protein level in sensitized nonasthmatics is linked to subsequent hyperresponsiveness to methacholine: the Odense Schoolchild Study.
Int Arch Allergy Immunol 121:129-136, 2000. ♦♦

Results of Delayed Hypersensitivity Testing Vary Between the Sexes

SKIN testing for delayed-type hypersensitivity is useful in screening for anergy and in testing for an immune response to infectious agents. The Multitest CMI skin test was designed to overcome the defects of previously used intradermal skin tests, but previous studies have suggested that women are less responsive than men to the antigens used in this test. This general population study sought to confirm the gender differences in response to the Multitest CMI.

The Multitest CMI skin test was administered to 297 subjects aged 18 to 64 years. The subjects were participants in a study of the immune effects of living near a hazardous waste site contaminated with organochlorine pesticides, although they had not complained of any symptoms or illness. Antigens tested including tetanus toxoid, diphtheria toxoid, *Candida*, *Trichophyton*, *Streptococcus*, and *Proteus*. Most subjects also underwent in vitro lymphocyte function testing using ➤➤

standardized methods of mitogen stimulation.

All immune markers studied were normal in most subjects, and the skin test results did not appear to be related to hazardous waste exposure. The rate of positive responses to skin testing was 80.4% for men vs 55.7% for women. Men had a higher frequency of positive responses to all 6 antigens. The increased frequency of response remained significant after controlling for other factors, including age, race, smoking, income, and pesticide exposure. The skin test results were unrelated to the mitogen stimulation assay results, overall or within the sexes.

Men show a higher frequency of positive results to the Multitest CMI skin test. Previous reports have also found gender differences, although not as pronounced as in this study. The reason for the difference is unknown, but it could limit the value of the Multitest CMI as an indicator of anergy in general population studies.

COMMENT: *Clinicians frequently use delayed-type hypersensitivity testing in evaluating cell-mediated immunity. While these skin tests are clearly imperfect, they are generally regarded as useful and delayed cost-effective. Although previous studies of skin test responses had not shown such significant differences, this important study of 300 adults raises key questions. If the gender differences in response are so great and have such little correlation with mitogen stimulation, perhaps we should re-evaluate the usefulness of these tests, particularly in women.*
A. M.
Vine MF, Stein L, Weigle K: Gender differences in response to the Multitest CMI skin test in the general population.
Ann Allergy Asthma Immunol 84:445-450, 2000. ♦♦

Inhaled Budesonide Aids Treatment of Acute Asthma in Infants

ACUTE episodes of wheezing and dyspnea are common in infants, and are sometimes persistent. Inhaled corticosteroids are effective in controlling respiratory symptoms in all age groups, and are increasingly used in younger children. This prospective study examined the clinical impact of adding nebulized budesonide to the treatment of infants hospitalized for acute wheezing and dyspnea. The study included 71 infants, aged 3 to 24 months, who required hospitalization for a severe, acute attack of wheezing and dyspnea. All received standard treatment with IV fluids, hydrocortisone, and nebulized fenoterol. In addition, one group received nebulized budesonide, 0.25 mg every 6 hours, while the other group received nebulized ipratropium bromide, 0.1 mg every 6 hours.

By 12 hours after admission, both groups showed significant reductions in clinical score and respiratory rate. This improvement was significantly faster with budesonide than with ipratropium. Mean length of hospital stay was 66 hours in the budesonide group and 93 hours in the ipratropium group.

Adding nebulized budesonide appears to hasten clinical improvement in infants with acute wheezing and dyspnea. In this young age group, inhaled corticosteroids may act more efficiently against underlying airway inflammation or help to increase β_2-adrenergic receptor function.

COMMENT: *In the treatment of acute asthma in babies, does the addition of nebulized corticosteroid add benefit on top of the usual regimen of bronchodilator, intravenous hydrocortisone, hydration, and oxygen? This group added nebulized budesonide 0.25 mg qid and found statistically significant improvement over the standard regimen.*
R. J. M.
Sano F, Cortez GK, Solé D, Naspitz CK: Inhaled budesonide for the treatment of acute wheezing and dyspnea in children up to 24 months old receiving intravenous hydrocortisone.
J Allergy Clin Immunol 105:699-703, 2000. ♦♦

Fexofenadine Reduces Side Effects of Bee Venom Immunotherapy

HYMENOPTERA venom immunotherapy is an effective treatment for patients with allergic reactions to Hymenoptera stings. However, this treatment is associated with a high rate of allergic side effects, particularly when immunotherapy with honeybee venom is given. Fexofenadine was evaluated for its ability to prevent side effects in patients receiving ultrarush bee venom immunotherapy. Fifty-seven such patients were randomized to receive either fexofenadine 180 mg or placebo, given on days 1, 8, 22, and 50 of the immunotherapy protocol. Twenty-eight patients in the fexofenadine group and 26 in the placebo group completed the study.

The fexofenadine group showed a significant reduction in the extension and duration of local reactions on day 1 of the study. Subjective and/or objective evidence of systemic allergic reactions occurred in 12 patients receiving fexofenadine and 9 receiving placebo. Although the overall number of systemic effects was not reduced, the histamine-induced cutaneous symptoms of pruritus, urticaria, and angioedema were less frequent with fexofenadine.

In patients receiving ultrarush bee venom immunotherapy, fexofenadine pretreatment can reduce local allergic reactions, as well as generalized symptoms of the urticaria and angioedema type. The overall occurrence of systemic allergic symptoms is not significantly reduced, however. There appears little risk that antihistamine pretreatment will mask the warning signs of impending severe allergic reactions.

COMMENT: *This double-blind, placebo-controlled study evaluated 57 patients with a history of systemic allergic reactions to honeybee stings and positive diagnostic confirmation. Bee venom immunotherapy by ultrarush protocol was given and patients randomized to be pretreated with 180 mg fexofenadine or* ➤➤

placebo. Pretreatment with fexofenadine reduced local reactions early in the treatment protocol as well as symptoms of urticaria and angioedema. No significant difference was noted in occurrence of systemic allergic symptoms. There was no evidence of masking any warning of a systemic reaction with pretreatment.
E. J. B.
Reimers A, Hari Y, Müller U: Reduction of side-effects from ultrarush immunotherapy with honeybee venom by pretreatment with fexofenadine: a double-blind, placebo-controlled trial. **Allergy** 55:484-488, 2000. ♦♦

Adding Salmeterol Plus Montelukast to Inhaled Steroids Improves Asthma Control

Adding an oral leukotriene receptor antagonist or inhaled long-acting β_2-agonist is beneficial for patients whose asthma is not adequately controlled by inhaled corticosteroids alone. The effects of adding both types of second-line therapy were evaluated in a single-blind, placebo-controlled, crossover trial.

The study included 12 patients with mild to moderate asthma. All had persistent symptoms despite an inhaled corticosteroid dose of greater than 400 µg/d; most were taking beclomethasone dipropionate. The patients continued their maintenance dose of inhaled corticosteroid throughout the study. In random order, they received single doses of oral montelukast sodium 10 mg; inhaled salmeterol xinafoate 50 µg; both oral montelukast 10 mg and inhaled salmeterol 50 µg; oral montelukast 10 mg plus inhaled salmeterol 100 µg; and placebo tablet plus placebo inhaler. Response was assessed by adenosine monophosphate (AMP) bronchial challenge and spirometry. Trough effects were measured at the end of the usual dosing interval.

All active treatments significantly improved the response to AMP bronchial challenge. The provocative concentrations of AMP causing a 20% or greater reduction in FEV_1 were 42 mg/mL with placebo, 106 mg/mL with montelukast alone, 115 mg/mL with salmeterol alone; 183 mg/mL with montelukast plus salmeterol 50 µg, and 247 mg/mL with montelukast plus salmeterol 100 µg. In combination, montelukast and salmeterol had numerically additive effects. The effects of montelukast plus salmeterol 100 µg were significantly greater than those of montelukast alone.

In asthma patients with suboptimal disease control on inhaled corticosteroid alone, adding a leukotriene receptor antagonist plus a long-acting β_2-agonist has additive benefits in terms of bronchoprotection and bronchodilation. This study finds a significant effect only with the combination including a 100 µg dose of salmeterol. This study evaluated just the response to a single dose of each drug or combination; further research is needed.

COMMENT: *While there is ample literature examining the effects of "adding-on" a second controller medication in patients with chronic asthma who are already receiving inhaled corticosteroid treatment, less is known about the benefits of multiple "add-ons." This study suggests that the bronchoprotection conferred by salmeterol and montelukast (assessed at trough after a single dose of each) is greater when both are given together. While all of us manage some patients with this combination, larger-scale clinical trials will be necessary to confirm the utility of this strategy.*
S. A. T.
Dempsey OJ, Wilson AM, Sims EJ, et al: Additive bronchoprotective and bronchodilator effects with single doses of salmeterol and montelukast in asthmatic patients receiving inhaled corticosteroids.
Chest 117:950-953, 2000. ♦♦

As-Needed Intranasal Fluticasone Relieves Rhinitis Symptoms

ANTIHISTAMINES are generally recommended for the treatment of mild allergic rhinitis, with intranasal corticosteroids reserved for more severe disease. Although effective, intranasal corticosteroids take longer to act than antihistamines and may not be efficacious when used on an as-needed basis. Many patients with mild allergic rhinitis may use treatment only when symptoms occur. This study evaluated the effectiveness of intranasal corticosteroids when used on an as-needed basis for symptoms of seasonal allergic rhinitis.

The randomized, double-blind trial included 56 patients with seasonal allergic rhinitis, enrolled in ragweed season. The patients were randomized to receive either fluticasone propionate nasal spray or placebo, and instructed to use their treatment as needed for 4 weeks. Patients were to administer two 50 µg sprays in each nostril no more than once daily.

Twenty-six patients in each group completed the study. During the treatment period, median symptom score on a scale of 0 to 9 was 8.5 in the placebo group vs 4.5 in the fluticasone group. On a quality-of-life questionnaire, steroid treatment was associated with significant improvements in sleep, non-nose/eye symptoms, activities, nasal symptoms, practical domains, and overall quality of life. Final eosinophil count was also lower with active treatment.

For patients with seasonal allergic rhinitis, fluticasone nasal spray effectively reduces symptoms when used on an as-needed basis. Previous studies have established that regular use of intranasal corticosteroids is more effective than as-needed use, however.

COMMENT: *The recommended treatment with intranasal corticosteroids suggests chronic dosing, as improvement takes up to 2 hours to occur and maximal benefit is reached only after several days of administration. Unfortunately, patients with allergic rhinitis may demonstrate poor adherence with regular therapy. Jen et al. demonstrate that fluticasone nasal spray on an as-needed basis can lead to both symptom relief and improved quality of life compared with placebo spray. The benefits may result from an anti-inflammatory effect. Although these agents work better when administered on a chronic basis, the study gives credence to the physician in prescribing them for seasonal* ➤➤

allergic rhinitis as needed. Studies need to be performed to determine whether antihistamines or intranasal corticosteroids give the best relief of allergic rhinitis symptoms when used as needed.
M. S. B.
Jen A, Baroody F, deTineo M, et al: As-needed use of fluticasone propionate nasal spray reduces symptoms of seasonal allergic rhinitis.
J Allergy Clin Immunol 105:732-738, 2000. ♦♦

Sputum Cysteinyl Leukotrienes Increase After Allergen Challenge

MODELS of provoked asthma have been utilized to study the actions of the eicosanoids—cysteinyl leukotrienes (cys LTs) and prostaglandins (PGs)—in asthma. Sputum induction has emerged as a noninvasive technique for use in studying airway inflammation. Changes in eicosanoid concentrations in response to allergen inhalation in patients with atopic asthma were studied in induced sputum.

The study included 14 patients with atopic asthma who developed a late asthmatic reaction to allergen challenge. Sputum induction was performed before and 24 hours after allergen inhalation. Sputum cytospins were prepared for differential cell counts, and cys LTs, PGD_2, and PGE_2 were measured in sputum supernatants. Median sputum eosinophil percentage increased from 1.9% at baseline to 16.4% at 24 hours. There was also a small but significant increase in sputum lymphocytes. The increase in sputum eosinophils was also accompanied by a rise in sputum cys LTs, from 3.45 to 11.95 ng/mL sputum. There was no significant change in sputum PG concentrations, however.

The noninvasive sputum induction technique documents a significant rise in sputum cys LTs 24 hours after allergen challenge in patients with atopic asthma. There is no accompanying rise in sputum PGs. The increase in sputum cys LTs is significantly associated with the change in sputum eosinophil percentage, suggesting that eosinophils are an important source of cys LTs in the airway.

COMMENT: *Previous studies have established the importance of cysteinyl leukotrienes in early asthmatic reactions following allergen inhalation. This study provides clear evidence for increased generation of these mediators during late-phase reactions and implicates the eosinophils as the cell of origin. Unlike bronchoscopic techniques, sputum induction is noninvasive, can easily be repeated in individual patients, and involves smaller and more uniform dilutions of lower airway secretions.*
J. R. B.
Macfarlane AJ, Dworski R, Sheller JR, et al: Sputum cysteinyl leukotrienes increase 24 hours after allergen inhalation in atopic asthmatics.
Am J Respir Crit Care Med 161:1553-1558, 2000. ♦♦

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