ALLERGYWATCH®

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

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

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Research Supports Allergen Avoidance Measures

THE availability of quantitative data on the role of allergens in atopy and allergy has highlighted the potential benefits of allergen avoidance. This article reviews the recent literature on allergen avoidance techniques.

A large body of evidence has shown that chronic asthma is strongly related to indoor allergen exposure. Mite, pet, and other allergens are found in large amounts in dust from beds, carpets, furniture, and clothing. However, it is difficult to relate current measures of allergen exposure to symptoms and to the effects of avoidance measures. The risk of sensitization is related to the level of allergen exposure, and allergen interventions are most effective if started early in life.

Though there is no simple "allergen avoidance" technique, a number of different strategies have been tested. The Isle of Wight study suggested that allergen avoidance helped in primary prevention of allergy in high-risk infants. A recent Japanese study confirmed this result, and more such trials are underway. Secondary prevention studies, seeking to induce remission and prevent persistence of allergic disease, have also given promising results. Tertiary interventions to reduce disease severity and improve asthma outcomes have yielded varying results, perhaps because of weaknesses in study design. Recent studies have shown that clinical manifestations of asthma can be reduced by having patients temporarily move from areas of high to low allergen exposure, or by interventions to reduce allergen exposure in the home. These studies have also demonstrated that it is possible to reduce domestic allergen exposure dramatically, and that patients will comply with recommended environmental and lifestyle changes if they are aware of the risks and benefits.

The most useful approaches to reduce house dust mite exposure are those aimed at reducing mite levels in bedding and clothing. Replacing carpets with smooth flooring and cleaning of hard surfaces are proba- ➤➤

CONTENTS

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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
- Journal of Occupational and Enviromental Medicine
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine

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bly useful. Possibly useful interventions are vacuuming, including wet or steam cleaning, and air cleaning devices such as air filters, air ionizers, and air conditioners. Acaricides are probably not useful. Building modification to reduce indoor humidity may be effective, but is difficult to implement. The most effective technique of pet allergen control is to remove the pet from the home; the next best option is to limit the animals to rooms with hard surfaces.

Despite research limitations, there is now considerable evidence that allergen avoidance measures are useful in the primary, secondary, and tertiary prevention of allergic disease. The importance of these techniques will probably increase with improvements in study design and in methods of assessing exposure and clinical outcomes.

COMMENT: *This nine-page review article is must reading for the practitioner interested in environmental allergen control. It summarizes evidence that allergen exposure affects disease outcomes and that primary, secondary, and tertiary interventions do work, in addition to reviewing the proven best practices for avoidance.*
R. J. M.
Tovey E, Marks G: Methods and effectiveness of environmental control.
J Allergy Clin Immunol 103:179-191, 1999. ♦♦

Mite Allergen Levels Are Higher on Synthetic Versus Feather Pillows

DESPITE a lack of supporting evidence, synthetic pillows are commonly recommended to reduce the risk of allergy to feather pillows. This study compared Der p 1 allergen accumulation on synthetic and feather pillows. The researchers placed pairs of new polyester and feather pillows together on the beds of 12 volunteers. Over the following year, they measured Der p 1 levels in dust samples taken from both pillows.

The mean Der p 1 level was 19.28 μg/g on synthetic pillows compared with 6.45 μg/g on feather pillows. The pillow Der p 1 level was strongly correlated with the baseline allergen concentration in the mattresses, but not with concentrations on carpeted floors.

Der p 1 allergen accumulates faster in synthetic pillows than in feather pillows, the study shows. The rate of allergen deposition depends on the immediate environment in which the pillows are placed. It is unclear why synthetic pillows have a faster rate of allergen accumulation, but the results do not support the recommendation of synthetic pillows for patients with house dust mite allergy.

COMMENT: *While many allergists routinely instruct patients to avoid feather pillows, pillow feather allergy is rare and recent evidence suggests that synthetic pillows contain more dust mites. This study further supports the argument that choosing synthetic pillows over feather pillows should* ***not*** *be done for the sake of reducing dust mite exposure.*
S. A. T.
Rains N, Siebers R, Crane J, Fitzharris P: House dust mite allergen (Der p 1) accumulation on new synthetic and feather pillows.
Clin Exp Allergy 29:182-185, 1999 ♦♦

Gelatin Sensitization Can Cause Anaphylaxis

TWO recent reports from Japan highlight the possibility of IgE sensitization to gelatin as a cause of anaphylaxis. A study analyzed the incidence of gelatin allergy among 366 patients with adverse reactions to monovalent measles, mumps, and rubella (MMR) vaccines containing 0.2% gelatin as a stabilizer. There were 34 episodes of anaphylaxis, 76 of urticaria, 215 of nonurticarial reactions, and 41 of local-only reactions. Serum testing of ➤➤

206 patients revealed IgE antibodies to gelatin in 93% of the anaphylaxis group and 56% of the urticaria group, compared with 9% of patients with generalized eruptions and none of those with local reactions. All patients whose vaccination history was available had received diphtheria and tetanus toxoid (DTaP) vaccine, almost always a gelatin-containing DTaP vaccine.

A separate case study describes a dialysis patient who developed a severe anaphylactic reaction on receiving a new recombinant human erythropoietin (EPO) product containing bovine gelatin as a stabilizer. She promptly recovered with treatment. The patient had no reaction to treatment with a conventional EPO product stabilized with human serum albumin, but had a repeat episode of anaphylaxis in response to another gelatin-containing EPO product. Testing revealed the presence of anti-bovine gelatin IgE but not anti-EPO IgE.

Gelatin has been regarded as an inert substance. The new study results suggest that most anaphylactic reactions to gelatin-containing MMR vaccines, and some cases of urticaria, can be attributed to IgE-mediated gelatin allergy. These cases of gelatin allergy may be caused by previous immunization with the gelatin-containing DTaP vaccine. Coupled with a case report of anaphylaxis in response to a gelatin-containing EPO product, the results underscore the potential for gelatin sensitization to cause anaphylaxis.

COMMENT: *These two articles confirm the sensitizing properties of gelatin used in vaccines and pharmaceutical agents. It is clear that anaphylactic reactions to the MMR vaccine are rarely due to egg proteins in the vaccine. Several reports, including the clinical analysis summarized here, document IgE sensitivity to gelatin as the cause. The case report shows that anaphylaxis to recombinant human EPO in an adult was caused by IgE sensitivity to gelatin used as a stabilizer. Physicians need to be aware of gelatin as a cause of severe anaphylactic reactions.*
M. S. B.

Nakayama T, Aizawa C, Kuno-Sakai H: A clinical analysis of gelatin allergy and determination of its causal relationship to the previous administration of gelatin-containing acellular pertussis vaccine combined with diphtheria and tetanus toxoids. J Allergy Clin Immunol 103:321-325, 1999.
Sakaguchi M, Kaneda H, Inouye S: A case of anaphylaxis to gelatin included in erythropoietin products.
J Allergy Clin Immunol 103:349-350, 1999. ♦♦

Long-Acting β_2-Agonists Reduce Albuterol Efficacy in Asthma Patients

ASTHMA patients receiving regular long-acting β_2-agonist therapy develop bronchoprotective subsensitivity, even if they are taking inhaled corticosteroids. This study evaluated the ability of high-dose albuterol, a short-acting β_2-agonist, to overcome bronchoprotective subsensitivity.

The randomized, crossover trial included 10 patients with stable asthma, mean FEV_1 77% of predicted. All were receiving inhaled corticosteroids, with a methacholine PD_{20} of less than 500 μg. Patients took part in three 9-day treatment periods with inhaled placebo twice daily; inhaled salmeterol dry powder, 50 μg twice daily; and inhaled formoterol dry powder, 12 μg twice daily. In each treatment period, methacholine challenge was performed three times: 1 hr after the first dose; after 7 days of treatment; and after 9 days, 1 hr after a single 1,600 μg inhaled dose of albuterol dry powder.

Geometric mean PD_{20} after the first dose was 78 μg with placebo compared to 266 μg with salmeterol and 318 μg with formoterol. As treatment continued, the level of bronchoprotection declined, though it was still superior to placebo at 7 days (68 versus 144 and 230 μg, respectively). In response to the single dose of albuterol at 9 days, PD_{20} was 889 μg with placebo, compared to 338 μg with salmeterol and 247 μg with formoterol.

For asthmatic patients with bronchoprotective subsensitivity caused by long-acting β_2-agonist therapy, the bronchoprotective effect of albuterol against methacholine challenge is significantly reduced. The results should prompt further studies in patients with acute asthma, who have higher bronchomotor tone. Despite the development of bronchoprotective subsensitivity, regular salmeterol or formoterol treatment offers a significant degree of residual bronchoprotection.

COMMENT: *It has become well-established by multiple investigations that continuous treatment with long-acting beta-agonists (salmeterol and formoterol) improves clinical control of asthma, but the protective effects against bronchial challenges decrease over time. This study shows that even high-dose albuterol (1,600 μg) before methacholine challenge does not overcome the beta-agonist subsensitivity induced by salmeterol or formoterol treatment. Does this mean patients would be subsensitive to rescue albuterol in clinical acute asthma? Stay tuned.*
R. J. M.

Lipworth BJ, Aziz I: A high dose of albuterol does not overcome bronchoprotective subsensitivity in asthmatic subjects receiving regular salmeterol or formoterol.
J Allergy Clin Immunol 103:88-92, 1999. ♦♦

AAAAI Reviews Data on Idiopathic Environmental Intolerances

IN this paper, the American Academy of Allergy, Asthma and Immunology (AAAAI) updates its position on idiopathic environmental intolerances (IEI), previously termed "multiple chemical sensitivities" or "environmental illness." By whatever name, IEI have been attributed to the failure of humans to adapt to modern synthetic chemicals. No precise definition or diagnostic criteria have been published. However, IEI are most almost always diagnosed in women, who usually have numerous symptoms involving multiple organ systems. Physical examination reveals no abnormalities. The patient relates the symptoms to environmental exposures, usually identified by odor, such as perfumes, pesticides, and solvents. Other triggering exposures include foods or food additives, drugs, electromagnetic fields, and dental mercury. The patient may be ➤➤

unable to point to the circumstances associated with symptom onset. A specific initiating event is more likely to be identified in workers compensation or personal injury cases.

Many different causes of IEI have been proposed. Clinical ecologists favor immunologic and toxicologic theories, while other authors propose a psychologic origin. The clinical ecologists respond that psychopathology is a result of the illness, not the cause. The diagnosis is made on the basis of patient history. There are no diagnostic criteria or validated diagnostic tests, though various tests may be performed.

Physicians who believe IEI symptoms result from environmental exposures may recommend an extreme avoidance program, sometimes with vitamins, IV gamma-globulin, and other supplemental treatments. Others recommend psychotherapy; there are few research data to support either approach. Some authors have suggested that IEI are part of a spectrum on nonphysical illnesses associated with multiple somatic complaints. Psychiatrists note similarities with somatoform/conversion disorders. However, IEI are distinct from well-characterized, diagnosable environmentally caused diseases.

This review highlights the difficulties of diagnosing and treating IEI. The symptoms are blamed on various environmental exposures; however, there have been no controlled studies to confirm these sensitivities. No immunologic or neurologic abnormality can be demonstrated, and no effective treatment has been identified. Current data do not support the theory that IEI symptoms are caused by environmental chemicals, foods, drugs, or other exposures.

COMMENT: *The AAAAI position papers provide us with up-to-date evidence-based reviews of hot topics. One of the hottest is what was formerly known as "environmental illness" or "multiple chemical sensitivity." These and similar syndromes have been renamed "idiopathic environmental intolerances" by experts convened by the World Health Organization. Physicians who advise patients, the legal system, and insurance companies on these syndromes will find this paper a valuable resource.*
R. J. M.

AAAAI Board of Directors: Idiopathic environmental intolerances. **J Allergy Clin Immunol** 103:36-40, 1999. ♦♦

Rhinitis Symptoms and Reactivity Lessen With Aging

A longitudinal study examined changes in skin test sensitivity and rhinitis symptoms over long-term follow-up. The study included 107 patients with rhinitis. Between 1969 and 1972, these patients underwent a battery of tests, including allergy scratch or intracutaneous testing and nasal provocation testing. An average of 23 years later, the patients underwent repeat evaluation, including skin prick testing and nasal allergen challenge. Mean age at follow-up was 51 years, with a range of 21 to 78 years. Changes in the results of allergy tests over time were compared with changes in rhinitis symptoms.

Skin test reactivity decreased significantly during follow-up, both in the series overall and among patients with initially confirmed allergy. The percentage of patients with one or more positive prick test reactions decreased from 89% among the youngest patients, to 72% in the middle age group, to 43% in the oldest patients. Among allergic patients, these percentages were 97%, 79%, and 63%, respectively. Though 92% of patients said they still had rhinitis symptoms, most reported that their symptoms were now milder. The changes in skin test reactivity were not significantly related to the changes in symptom severity.

This study suggests that, among patients with rhinitis, skin prick test reactivity declines with aging. Rhinitis symptoms become less severe with time also. However, the decrease in symptom severity appears independent of the change in prick test sensitivity. The results suggest that changes in skin test reactivity do occur, and that repeated skin testing can give useful information in selected patients with evidence of new allergy.

COMMENT: *The authors provide important insights into the natural history of allergic disease. In their study, 107 adults with allergic rhinitis underwent follow-up skin testing and nasal provocation 23 years following their initial evaluation. While previous reports had documented decreased rhinitic symptoms with age, this study demonstrated that diminished skin test reactivity and symptom changes may not be associated. Since most clinicians are dealing with an ever-increasing aging population, this study provides clinically relevant observations. In an accompanying editorial, Dr. I. L. Bernstein addresses other important issues with regard to aging and allergic disease.*
A. M.

Simola M, Holopainene E, Malmberg H: Changes in skin and nasal sensitivity to allergens and the course of rhinitis; a long-term follow-up study. Ann Allergy **Asthma Immunol** 82:152-156, 1999. ♦♦

Cellulase-Induced Asthma Reported in a Textile Worker

OCCUPATIONAL allergy caused by cellulase—enzymes that degrade cellulose to glucose—has been previously reported among laboratory workers, pharmaceutical employees, and bakers. The first published case of cellulase-induced occupational asthma in a textile industry worker is reported.

The 23-year-old man had previously worked at a textile company, using cellulase to remove fuzz from clothes. He had a 19-month history of cough and dyspnea, worse at night and better when he was on vacation. Skin prick testing suggested the patient was atopic. He did not react to any of the dyes he was exposed to at work, but had a strongly positive reaction to cellulase extract. Bronchoprovocation testing with cellulase extract induced an early asthmatic response. Enzyme-linked immunosorbent assay showed serum specific IgE and specific IgG_4 antibodies to cellulase. Sodium dodecyl sulfate polyacrylamide gel electrophoresis and electroblotting studies detected eight IgE-binding components—with molecular weights of 6 to 97.5 kD—within the cellulase extract. With avoidance of cellulase and use of antiasthmatic medications, the patient's symp- ➤➤

toms resolved and his hyperresponsiveness to methacholine decreased.

This case of cellulase-induced occupational asthma in a textile worker suggests an IgE-mediated reaction. The pathogenic roles of specific IgG and IgG_4 antibodies in occupational asthma remain to be determined.

COMMENT: *Cellulase is a known high-molecular-weight sensitizing agent than can result in occupational asthma. The authors highlight the first reported case of occupational asthma due to cellulase in the textile industry. Since the number of potential at-risk workers is large, clinicians should be aware of this potential association.*
A. M.
Kim H-Y, Nahm D-H, Park H-S, Choi D-C: Occupational asthma and IgE sensitization to cellulase in a textile industry worker.
Ann Allergy Asthma Immunol 82:174-178, 1999. ♦♦

Budesonide Is Effective in Infants and Young Children with Asthma

THE glucocorticosteroid budesonide was studied for use in infants and young children with moderate, persistent asthma. Four hundred eighty such patients, aged 6 months to 8 years, were randomized to receive 12 weeks of treatment with placebo or one of four different budesonide inhalation suspension (BIS) dosages: 0.25 mg once daily (qd), 0.25 mg twice daily (bid), 0.5 mg bid, or 1.0 mg qd. At baseline, all patients were receiving regular medication for asthma control; 31% were receiving inhaled corticosteroids, which were discontinued for the study. Efficacy outcome measures included asthma symptom scores, need for rescue medications, and study dropout because of worsening asthma. In children able to perform pulmonary function tests, peak flow measurements were obtained. Adverse events were recorded, and cortisol testing was performed in some patients.

All four BIS groups achieved good asthma control. This included the 0.25 mg qd dosage, though this group met fewer efficacy measures than those receiving higher dosages. By 2 weeks of BIS treatment, daytime and nighttime symptom scores were significantly different than in the placebo group. Among tested children, most of those receiving BIS showed improved peak flow measurements. However, only the 0.5 mg bid group showed a significant improvement in FEV_1 compared with the placebo group. Safety measures were not significantly different with BIS versus placebo.

This multicenter randomized trial shows the safety and efficacy of BIS treatment for infants and young children with moderate, persistent asthma. Budesonide is effective across a range of dosages, including once-daily dosing. It is the first nebulizable corticosteroid with the potential to control asthma in the youngest patients.

COMMENT: *Budesonide works for asthma, it appears safe even in children as young as 6 months, it can be given on a once- or twice-a-day schedule, and it can be made into a nebulizer solution. The only question that remains is, when will we able to get our hands on some?*
J. A. P.
Baker JW, Mellon M, Wald J, et al: A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants.
Pediatrics 103:414-421, 1999. ♦♦

Early Day Care Reduces Risk of Allergy

IF early childhood infections reduce the subsequent risk of allergies, then early day-care attendance—with resultant cross-infection—should reduce the risk of atopy. This cross-sectional study analyzed atopy rates among children who started day care at varying ages. The study included 2,471 German children in three age groups: 5 to 7, 8 to 10, and 11 to 14 years. Data on the children's allergies, day care attendance, and other factors were gathered from parental questionnaires. Skin prick testing and serum allergen-specific IgE antibody measurement were performed to assess sensitization.

Among a subgroup of 669 children from families including three or fewer members, the prevalence of atopy was lower for children starting day care at an earlier age, compared with those starting at a later age. Compared with children starting day care at age 6 to 11 months, the adjusted odds ratio of a positive skin prick test was 1.99 (95% confidence interval 1.08 to 3.66) for those starting at 12 to 23 months, and 2.71 (95% confidence interval 1.37 to 5.40) for those starting at age 24 months or older. Early day care attenders also had less hayfever and eye irritation later in life. Age of entry to day care had no effect on atopy risk among children from larger families.

Among children from small families, starting day care early in life is associated with a reduced prevalence of later atopy. The data support the hypothesis that infections during early childhood have a protective effect against asthma later in life. The associations observed in this study are not explained by selection bias.

COMMENT: *One hypothesis forwarded to explain the increasing prevalence of childhood allergies is a decline in exposure to infections early in life. This study investigated the association between preschool attendance at day nursery and atopy in later life in a cross-sectional survey of children aged 5 to 14 years in eastern Germany. Children from small families who entered day nursery at age 6 to 11 months had a lower prevalence of atopy than those who entered at an older age. These results are in accord with those of Hurwitz et al., on the risk of respiratory illness associated with age and number of siblings in a U.S. study (Pediatrics 87:62-69, 1991).*
E. J. B.
Krãmer U, Heinrich J, Wjst M, Wichmann H-E: Age of entry to day nursery and allergy in later childhood.
Lancet 352:450-454, 1998. ♦♦

Dimensions of Asthma Should Be Measured Separately

FACTOR analysis—a statistical technique in which multiple disease parameters can be reduced to a few independent factors made up of associated parameters—was used to assess the interdependence of various dimensions of asthma. The study included 99 patients with clinically stable asthma, all of whom underwent traditional tests of asthma severity: spirometry, sputum induction, and histamine inhalation. Factor analysis was then performed to evaluate the interrelationships among reversible airway obstruction, bronchial hyperresponsiveness (BHR), and eosinophilic inflammation of the bronchial tree.

As a group, the patients had unobstructed breathing, with a mean FEV_1 of 91%; low bronchial reversibility, with a mean 8% increase in FEV_1 after 2-agonist administration; and BHR, with a geometric mean histamine PC_{20} FEV_1 value of 0.98 mg/mL. Thirty-eight percent of patients had a sputum eosinophil differential count within the range of normal, while 22% had a normal sputum eosinophil cationic protein (ECP). Factor analysis identified three factors accounting for 75% of the observed variability. Factor I comprised airway function measures and age, while PC_{20} FEV_1 and $_2$ response loaded on factor II and sputum eosinophil cationic protein and sputum eosinophils loaded on factor III. A further analysis grouping patients by randomization, presence of airway obstruction, degree of BHR, percentage of sputum eosinophils, or sputum ECP concentration yielded similar results.

These factor analyses suggest that measures of airway obstruction, BHR, and airway inflammation constitute separate dimensions of asthma severity. Routine assessment of patients with chronic asthma should include all three dimensions. The physiologic and inflammatory measures used to describe asthma severity do not overlap.

COMMENT: *Three components of asthma—airway inflammation, bronchial hyperresponsiveness, and airway function—are thought to be closely related to the severity of asthma. This study clearly shows the variability of these three parameters in stable asthmatics. Clinicians should therefore include all three measures in the clinical evaluation of the asthmatic patient.*
M. S. B.

Rosi E, Ronchi MC, Grazzini M, et al: Sputum analysis, bronchial hyperresponsiveness, and airway function in asthma: results of a factor analysis.
J Allergy Clin Immunol 103:232-237, 1999. ♦♦

Salmeterol Prevents Exercise-Induced Bronchospasm in Asthmatic Children

PRETREATMENT with albuterol prevents exercise-induced bronchospasm (EIB) in children with asthma, but its protective effect lasts only 2 to 3 hr. Salmeterol powder given via Diskus inhaler was evaluated for the prevention of EIB in pediatric asthma patients. The randomized, crossover trial included 26 children, aged 4 to 11 years, with mild to moderate asthma and a history of EIB. All children performed treadmill exercise challenges on separate days: once after taking 25 μg of salmeterol powder, once after 50 μg of salmeterol powder, once after 180 μg of albuterol aerosol, and once after placebo. On each day, serial measures of FEV_1 were obtained before treatment and after exercise challenges peformed 1, 6, and 12 hr after treatment. The treatments were compared for efficacy and safety.

Mean minimum percent of predicted FEV_1 after the 1 hr exercise challenge was 87% with salmeterol 25 μg, 86% with salmeterol 50 μg, 91% with albuterol, and 75% with placebo. Mean minimum percent of predicted FEV_1 after the 6 hr challenge was 91% with salmeterol 50 μg compared with 78% for both albuterol and placebo. After the 12 hr challenge, the value was 87% with salmeterol 50 μg versus 74% with albuterol and 77% with placebo. The 25 μg dose of salmeterol was similar to albuterol and placebo after the 6 hr challenge, but significantly better (with a value of 88%) after the 12 hr challenge. Throughout the study protocol, the two doses of salmeterol produced similar spirometric values. There were no drug-related adverse events, and no clinical or laboratory evidence of other safety problems.

Salmeterol 50 μg given via Diskus inhaler provides up to 12 hr protection against EIB in children with mild to moderate asthma. This is a significantly longer-lasting protective effect than with 180 μg albuterol aerosol. Salmeterol can be given on a less-frequent dosing schedule, a significant clinical advantage over shorter-acting bronchodilators.

COMMENT: *Since the introduction of salmeterol, its role in the treatment of EIB has been poorly understood. In this important clinical study of 26 children aged 4 to 11 years, both doses of salmeterol appeared safe and effective in the prevention of EIB. This study confirmed that albuterol is preferred for those who exercise in the first hour after use. However, from 1 to 12 hours, salmeterol is more effective. Because children's exercise patterns are unpredictable, a single 50 μg dose of salmeterol by Diskus appears safe and effective.*
A. M.

Blake K, Pearlman DS, Scott C, et al: Prevention of exercise-induced bronchospasm in pediatric asthma patients: a comparison of salmeterol powder with albuterol.
Ann Allergy Asthma Immunol 82:205-211, 1999. ♦♦

Bronchial Inflammation Is Greater Than Nasal Inflammation in Patients with Asthma and Rhinitis

ASTHMA and rhinitis frequently occur together. Both are involved with inflammation, and they share some causative factors. This study compared inflammatory markers in the nasal and bronchial mucosa of asthmatic patients with perennial rhinitis. The study included 15 untreated patients with allergic asthma and perennial rhinitis, 6 corticosteroid-dependent (CSD) asthmatics, and 6 controls. Nasal and bronchial biopsies were obtained for comparison of inflammatory parameters, such as eosinophilic infiltration, epithelial shedding, and reticular basement membrane thickness. ➤➤

Both the nasal and bronchial biopsies showed higher eosinophil numbers in untreated asthmatics than in controls or CSD asthmatics. Within the untreated asthmatic group, eosinophil number was higher in the bronchial biopsies than the nasal biopsies. The two asthmatic groups had greater reticular basement membrane thickness than the control group. In addition, both asthmatic groups had greater reticular basement membrane thickness in the bronchial biopsies than the nasal biopsies. The untreated asthmatic patients had greater bronchial epithelium shedding than the controls or CSD asthmatics. Within the untreated asthmatic group, bronchial epithelium shedding was greater than nasal epithelium shedding.

In patients with concomitant asthma and rhinitis, various inflammatory parameters are more elevated in the bronchial mucosa than in the nasal mucosa. The findings in CSD asthmatics suggest that oral corticosteroids reduce eosinophilic inflammation in both the bronchial and nasal mucosa. Studies of the antiadhesion molecule episialin suggest that mechanisms other than simple eosinophilic shedding may be involved in bronchial epithelial shedding.

COMMENT: *This study suggests that although asthma and rhinitis often coexist, they have dissimilar inflammatory profiles. The extent of eosinophilic inflammation of reticular basement membrane thickness and of epithelium shedding is greater in bronchial than in nasal mucosa of asthmatic patients with perennial rhinitis.*
J. B.-M.

Chanez P, Vignola AM, Vic P, et al: Comparison between nasal and bronchial inflammation in asthmatic and control subjects.
Am J Respir Crit Care Med 159:588-595, 1999. ♦♦

Maternal Smoking Affects Infant Respiratory Morbidity

THIS study examined the association between airway function and subsequent symptoms of wheezing in infants, including the contribution of a family history of asthma and maternal smoking during gestation. The analysis included 101 term infants who underwent airway function testing before 13 weeks of age and before any respiratory illness developed. Of these, 28 went on to have at least one episode of wheezing during their first year of life.

The infants with wheezing had significantly lower specific airway conductance than those without wheezing. Specific airway conductance was also reduced in infants who had a first-degree relative with asthma. Infants whose mothers smoked during pregnancy did not have reduced airway conductance; however, they did have significantly increased airway resistance. The odds of wheezing were increased approximately 4-fold by a family history of asthma, and nearly 5-fold by maternal smoking during pregnancy.

Consistent with previous studies, these results show that infants with impaired airway function are more likely to develop wheezing during the first year of life. A family history of asthma may be associated with abnormalities of airway function or tone, thus predisposing to wheezing. Maternal smoking during pregnancy appears to be an important and preventable risk factor for respiratory morbidity in infancy. More study is needed to see if the reductions in specific airway conductance demonstrated in this study persist after 1 year of age.

COMMENT: *This study confirms prior reports that impaired premorbid airway function precedes and predicts wheezing in the first year. Genetic and environmental factors—especially parental smoking—are significant factors in lung development and may account for impairment in airway function in adult life.*
J. B.-M.

Dezateux C, Stocks J, Dundas I, Fletcher ME: Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma.
Am J Respir Crit Care Med 159:403-410, 1999. ♦♦

E-selectin Reflects Disease Activity in Atopic Dermatitis

IN addition to total serum IgE, useful markers of disease activity in atopic dermatitis (AD) include soluble interleukin-2 receptor, soluble intercellular adhesion molecule-1, eosinophil cationic protein, and CD14. The cell-surface adhesion molecule E-selectin plays a role in leukocyte infiltration into inflamed tissue, and is an important determinant of the degree of inflammatory infiltration. E-selectin was evaluated as an indicator of disease activity in AD.

The study included 14 patients with severe AD. For 4 weeks before the study, they received no therapy with immunosuppressive agents, retinoids, interferon, phototherapy, or oral steroids. All were treated with cyclosporin A (CsA), 4.5 mg/kg/bid, using either the old Sandimmun formulation or the new Neoral microemulsion. Before and after 16 weeks of CsA therapy, soluble E-selectin (sE-selectin) levels were measured using an enzyme-linked immunosorbent assay (ELISA).

Compared with healthy controls, AD patients had significantly elevated sE-selectin levels at baseline. Cyclosporin A treatment was followed by a significant reduction in sE-selectin levels. This change was significantly associated with reductions in markers of disease severity.

E-selectin appears to be a useful marker of disease activity in AD. As patients' clinical condition improves in response to CsA, their sE-selectin levels decrease significantly. E-selectin may answer the need for a simple serologic test for use in monitoring disease activity in AD patients.

COMMENT: *Fourteen patients with severe atopic dermatitis and 41 healthy controls were studied. Soluble E-selectin was measured by ELISA both 2 weeks before therapy with cyclosporin A and after 16 weeks of treatment.. Soluble E-selectin was elevated in patients with atopic dermatitis. Cyclosporin resulted in improvements in clinical condition and was associated with a significant decrease in sE-selectin levels.*
E. J. B.

Kãgi MK, Joller-Jemelka H, Wåthrich B: Soluble ➤➤

E-selectin correlates with disease activity in cyclosporin A-treated patients with atopic dermatitis. **Allergy** 54:57-63, 1999. ♦♦

Authors Urge Exceptions to Informed Consent in Randomized Trials

THIS editorial proposes guidelines under which informed consent could be waived for participants in randomized, controlled trials. Under current guidelines, physicians can offer new treatments to individual patients without informed consent, yet must obtain consent if the patients are participants in a randomized trial. The doctrine of informed consent plays an important role in protecting patients' interests. Whereas general informed consent is regarded as part of the patient-physician relationship, specific informed consent is needed for interventions involving a high risk-benefit ratio. The authors believe that, for the purpose of clinical trials, the need for informed consent should be based on the risk of the procedure, the available alternatives, and the degree to which patients would be expected to have preferences regarding the various options.

Under the authors' proposed criteria, informed consent would not be waived unless all of the treatments offered could be used without specific informed consent, as in a trial comparing two existing drugs. The treatments should not differ significantly in their degree of risk, and it must be truly uncertain which is superior. Regardless of the differences between treatments, there should be no reason why a reasonable person should prefer one treatment over the other. To ensure the validity of the reasonable-person standard, requests for waiver of informed consent should be submitted to the institutional review board. Finally, patients should understand the informed consent guidelines being used at the treating center, thus enabling them to seek additional information or to seek care elsewhere.

In arguing against the need for specific informed consent for all randomized trials, the authors point out that informed consent is not a goal in itself. Their proposed criteria for wavier of informed consent respect the patient's right to self-determination and minimize the risk to those involved, while offering the chance of real benefits to society.

COMMENT: *In this provocative review of the complicated issue of informed patient consent for nonstandard therapies, the authors note that individual practitioners can legally use procedures or drugs in off-label ways in individual patients without informed consent. Contrast this to the elaborate requirements for consent in clinical trials. As the authors say, "physicians can do almost anything they want in the name of therapeutic innovation, but only if there is no attempt to gain systematic knowledge from the intervention." Sublingual drop therapy, chiropractic therapy, and other alternative therapies come immediately to mind. So do small incremental changes in standard therapies. Where do we draw the line?*
R. J. M.
Truog RD, Robinson W, Randolph A, Morris A: Is informed consent always necessary for randomized, controlled trials? **N Engl J Med** 340:804-807, 1999. ♦♦

Inhaled Budesonide Reduces Diverse Inflammatory Markers in Asthma

A randomized, crossover trial was performed to assess the effects of inhaled budesonide on lung function and various airway inflammatory markers in asthma patients. The study included 14 patients with mild asthma who were being treated with β_2-agonist therapy only. They were randomized to receive 4 weeks of treatment with inhaled budesonide, 800 µg twice daily via Turbohaler or matched placebo; after a 4-week washout period, they were crossed over to the other treatment. In addition to lung function studies, various indicators of airway inflammation were assessed, including airway responsiveness to methacholine, exhaled nitric oxide (measured by chemiluminescence analyzer), eosinophils in induced sputum, and bronchoalveolar lavage (BAL).

Budesonide therapy was followed by significant increases in FEV_1 and in methacholine PC_{20}. At the same time, exhaled nitric oxide decreased significantly. Steroid treatment was also associated with reduced eosinophil counts in induced sputum and airway biopsies, though there was no change in BAL eosinophil count. However, there were only weak correlations between most of these changes. Posttreatment eosinophils in biopsy sections and BAL were significantly correlated with log PC_{20} methacholine.

This study demonstrates the effectiveness of inhaled budesonide as an anti-inflammatory agent in patients with mild asthma. This treatment significantly improves airway function and reduces markers of airway inflammation. The various markers appear to represent different underlying mechanisms of the inflammatory response, all of which are reduced by inhaled steroids. The absence of more significant relationships could result from a lack of statistical power to detect small differences within the steroid-naive patients studied.

COMMENT: *This study demonstrates that budesonide is an effective anti-inflammatory agent in mild asthma. It is capable of improving airway function and airway reactivity while significantly reducing inflammatory parameters, including nitric oxide, sputum eosinophils, and bronchial mucosal histology. However, the results show a relatively weak association between these changes, suggesting that they represent different mechanisms underlying the inflammatory response, all of which are inhibited by inhaled steroids.*
J. B.-M.
Lim S, Jatakanon A, John M, et al: Effect of inhaled budesonide on lung function and airway inflammation: assessment by various inflammatory markers in mild asthma. **Am J Respir Crit Care Med** 159:22-30, 1999. ♦♦

GM-CSF May Play a Role in Eosinophil Recruitment to Nasal Mucosa

IN a previous study, the authors found that topical steroid administration reduced allergen-induced late nasal responses and the accompanying tissue eosinophilia. Granulocyte/macrophage-colony stimulating factor (GM-CSF) was evaluated for its involvement in the late response, and its inhibition by topical corticosteroid.

Eighteen patients with seasonal allergic rhinitis were treated for 6 weeks with either fluticasone propionate or matched placebo nasal spray, twice daily. The patients then underwent nasal allergen provocation, before and 24 hr after which nasal biopsy specimens were taken. Expression of GM-CSF mRNA was assessed by immunohistochemistry and in situ hybridization.

The postchallenge nasal biopsies showed increased numbers of T-lymphocytes and eosinophils. They also showed a 5-fold increase in cells expressing mRNA for GM-CSF. About 40% of cells expressing GM-CSF mRNA were co-localized to cells positive for CD68 and 40% to T cells, while 20% were co-localized to eosinophils. The number of CD3-positive and major basic protein-positive cells expressing GM-CSF mRNA decreased with topical steroid treatment. At the same time, the percentage of GM-CSF-expressing macrophages increased.

Granulocyte/macrophage colony-stimulating factor appears to play at least some role in eosinophil recruitment to the nasal mucosa after allergen challenge. The allergen-induced late nasal response, and the associated eosinophilia, is inhibited by topical nasal corticosteroid. This treatment effect could be related to reductions in T-lymphocyte GM-CSF or in autocrine production of GM-CSF by eosinophils. Treatments to inhibit GM-CSF or its receptors could offer a new therapeutic approach to allergic rhinitis.

COMMENT: *Understanding the molecular events responsible for developing and maintaining chronic allergic inflammation has great clinical relevance as a new "biotech" era emerges, providing very focused therapeutic options. This study suggests that the cytokine GM-CSF may play a more important role than previously thought in the recruitment of eosinophils to the nasal mucosa during the late phase of an allergen challenge.*
S. A. T.

Nouri-Aria KT, Masuyama K, Jacobson MR, et al: Granulocyte/macrophage-colony stimulating factor in allergen-induced rhinitis: cellular localization, relation to tissue eosinophilia and influence of topical corticosteroid. **Int Arch Allergy Immunol** 117:248-254, 1998. ♦♦

Influenza Vaccine Prevents Infection and Reduces Sick Days in Health Care Workers

THIS 3-year randomized trial sought to document the benefits of influenza vaccination for health care professionals. The study included a total of 264 healthy, hospital-based health care professionals, mostly residents. Forty-nine subjects participated for two influenza seasons and 24 for three seasons. In each season, the subjects were randomized to receive trivalent influenza vaccine or a control—either meningococcal vaccine, pneumococcal vaccine, or placebo. The analysis included 359 person-winters of serologic surveillance and 4,746 person-weeks of illness surveillance.

Serologic evidence of influenza A or B infection developed in 13% of controls versus 2% of vaccinated subjects. Vaccination had an efficacy rate of 88% against serologically detected influenza A and 89% against influenza B. Reported days of febrile respiratory illness were 29/100 subjects receiving influenza vaccination compared with 41/100 for controls. Days of absence were 10/100 and 21/100, respectively.

Influenza vaccine confers a relative 88% reduction in serologically defined influenza A or B infection in healthy, young health care workers. Vaccination also appears to reduce cumulative days of illness and absence. Health care workers should receive yearly influenza vaccinations.

COMMENT: *This study, performed at Johns Hopkins and Sinai Hospitals in Baltimore, documents what we know intuitively—that health care workers should receive their influenza immunizations yearly without fail. The 13% risk of contracting influenza type A or B infection was significantly reduced, as was work absenteeism. It is hoped that clinical allergists, knowing well the risk of influenza infection in patients with asthma, are compliant with their own immunizations.*
S. R. W.

Wilde JA, McMillan JA, Serwint J, et al: Effectiveness of influenza vaccine in health care professionals: a randomized trial. **JAMA** 281:908-913, 1999. ♦♦

TMA Occupational Asthma Linked to Increased Atopy

OCCUPATIONAL asthma can be caused by trimellitic anhydride (TMA) and other low-molecular-weight industrial compounds. This case-control study evaluated the association between atopy and TMA occupational asthma. The study included 16 workers with TMA-induced asthma and 44 control workers with similar exposures. Both groups underwent specific IgE measurements for cat, dust mite, rye grass, and ragweed antigens.

Atopy was detected in 56% of the workers with TMA occupational asthma versus 29% of controls. There was a trend toward increased atopy in the cases, but the difference was not statistically significant. The odds ratio for TMA asthma among atopic subjects was 3.17.

Atopy may be a risk factor for TMA occupational asthma, the findings suggest. However, the association is not strong enough for use in screening workers for risk of TMA occupational asthma. The authors call for further studies in larger populations to clarify the role of atopy in occupational asthma caused by low-molecular-weight compounds such as TMA.

COMMENT: *The acid anhydrides are a group of reactive low-molecular-weight substances that can cause occupational asthma (OA). Previous studies have failed to show an association with low-molecular-weight chemical-induced OA and atopy. In this case-control study, there appears to be a trend toward greater atopy* ➤➤

in individuals with OA secondary to TMA. Though this observation is interesting, the presence or absence of atopy cannot be used as a screening tool in the clinical diagnosis of OA due to TMA.
A. M.
Sikora R, Harris KE, Kenamore B, Grammer LC: Immunoglobulin E antibody against environmental allergens in subjects with trimellitic anhydride-induced asthma. **J Occup Environ Med** 41:190-194, 1999. ♦♦

Bupropion Increases Smoking-Cessation Rates

THIS study compared the effectiveness of two pharmacologic aids to smoking cessation—nicotine patches and the antidepressant bupropion—alone and in combination. The randomized trial assigned 244 smokers to sustained-release bupropion, 244 to nicotine patches, 245 to bupropion plus nicotine patches, and 160 to placebo.Clinically depressed patients were excluded. The bupropion dosage was 150 mg/day for 3 days, then 150 mg twice daily. The transdermal nicotine dosage was started at 21 mg/day, tapering to 7 mg/day. All treatments lasted 9 weeks.

One-year rates of abstinence from smoking were 36% with bupropion only, 30% with bupropion plus nicotine patches, 16% with nicotine patches only, and 16% with placebo. All active treatments were associated with less severe withdrawal symptoms and less weight gain, compared with placebo. Patients in the combined-treatment group had the least weight gain. Thirty-five percent of patients stopped taking one or both medications. Insomnia and headache were the most frequent adverse effects.

Sustained-release bupropion is an effective aid to smoking cessation, with or without nicotine patches. Long-term smoking cessation rates are significantly higher with bupropion than with either nicotine patches or placebo, which did not differ significantly in this study.

COMMENT: *This multicenter study (sponsored by the manufacturer of bupropion [Zyban]) compared smoking-cessation results after bupropion versus placebo, with and without nicotine patches. Education and monthly follow-up counseling were provided to all. The abstinence rate after 1 year of follow-up was greatest in bupropion-treated patients, with or without patches. The patch-only group had no better success than the placebo group. Health care insurers, some of whom have been reluctant to cover these agents, should take note.*
R. J. M.
Jorenby DE, Leischow SJ, Nides MA, et al: A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation.
N Engl J Med 340:685-691, 1999. ♦♦

Itching May Not Be the Cause of Sleeplessness in Atopic Dermatitis

POLYSOMNOGRAPHIC studies were performed to evaluate the sleep patterns of children with atopic dermatitis. The study included 14 children with AD in remission, when sleep problems related to scratching should be less common. The children, mean age 6 years, had no other medical or psychiatric illness. Nine controls with mild snoring but no evidence of sleep-related respiratory disturbance were studied for comparison. During all-night polysomnography, scratching movements were assessed using electrodes placed on the hands and fingers.

The AD patients and controls were similar in terms of sleep latency, total sleep time, and sleep efficiency. However, the frequency of arousals and awakenings was significantly higher in the AD group: 24 ± 8 per hour, compared with 15 ± 6 per hour in the control group. Only about 15% of these episodes could be ascribed to scratching. The remainder were unrelated to apnea, jerks, or any other particular polysomnographic event.

Even when their disease is in remission, children with AD show abnormally fragmented sleep. The arousals and awakenings do not appear to be related to scratching, or to any other sleep-related abnormality. Sleep disturbance in AD children may be reflected by longer afternoon naps and increased daytime sleepiness, which may lead to learning disabilities or behavioral problems.

COMMENT: *It has always been believed that children with AD have sleep disturbances because of severe itching through the night. This Israeli study suggests that there may be other causes of sleep fragmentation in AD, as these children continued to have sleep problems even after their atopic dermatitis went into remission. Further research into sleep abnormalities in children with AD is needed to help improve sleep for these patients and their parents.*
M. S. B.
Reuveni H, Chapnick G, Tal A, Tarasiuk A: Sleep fragmentation in children with atopic dermatitis.
Arch Pediatr Adolesc Med 153:249-253, 1999. ♦♦

Case Reports Show Heterogeneity of Mastocytosis

FOUR main categories of mastocytosis have been identified: indolent, hematologic disorder, aggressive, and mastocytic leukemia. The presentation of mastocytosis varies widely, as do the prognostic implications. Three case reports illustrating the varying findings and outcomes of mastocytosis are presented.

Case 1 involved an alcoholic woman with systemic mastocytosis who underwent successful orthotopic liver transplantation. No mast cell infiltrate was detected in the liver, before or after transplantation. The risks of performing surgery in a patient with mastocytosis were carefully assessed preoperatively, focusing on the potential for mast cell degranulation. Case 2 was a woman with an apparent predisposition to cutaneous mastocytosis. Her disease followed an indolent course; both the patient and her mother were diagnosed as having urticaria pigementosa in adulthood. Case 3 was a woman initially diagnosed as having systemic mastocytosis. Within 1 year, she died of mast cell leukemia. Findings possibly associated with aggressive disease includ- ➤➤

ed rapid progression of symptoms and an initially large burden of mast cell infiltrates in the intradmedullary space on bone marrow biopsy.

The clinical presentation and final outcome of systemic mastocytosis can vary widely, from a relatively indolent course to rapid progression to mast cell leukemia. Promising avenues for future research include early definition of c-kit receptor mutations. Such studies may provide a better understanding of the molecular basis of systemic mastocytosis, leading to better-targeted therapies and an improved prognosis.

COMMENT: *This report discusses three cases of systemic mastocytosis distinguished by novel aspects of disease: the first a successful liver transplant in a patient with mastocytosis, the second a case of potential hereditary mastocytosis, and the third a patient who had clinical features predictive of a poor clinical course, who then had progression to mast cell leukemia.*
M. S. D.

Pauls JD, Brems J, Pockros PJ, et al: Mastocytosis: diverse presentations and outcomes.
Arch Intern Med 159:401-405, 1999. ♦♦

Angioedema Can Be Caused by Angiotensin II Receptor Antagonists

THIS report describes a rare patient with angioedema caused by the angiotensin II receptor antagonist losartan. The patient, a 49-year-old woman, had been taking losartan 50 mg/day for hypertension. She was also taking simvastatin, 10 mg/day, for hyperlipoproteinemia. The patient developed angioedema of the face and generalized urticaria, which had never occurred previously. At the same time, she had unilateral neural and motor deficiencies on the right side of the face and in the right arm and leg.

The angioedema resolved within 3 days after discontinuation of losartan and treatment with oral prednisolone, 50 mg/day. The symptoms of transient ischemic attack cleared almost completely within 1 day. Antihypertensive medication was restarted with a calcium antagonist.

This patient's angioedema was probably caused by a reaction to losartan. Episodes of angioedema related to angiotensin-converting enzyme inhibitors are associated with increased plasma bradykinin concentrations. However, the kallikrein-kinin system is unaffected by angiotensin II receptor antagonists. This is the first known case of angioedema induced by an angiotensin II receptor antagonist, in association with a transient ischemic attack.

COMMENT: *Angioedema is a rare adverse drug reaction to angiotensin II receptor antagonists. The latter do not interfere with the kallikrein-kinin system and therefore are unassociated with the increased plasma bradykinin seen in angioedema caused by conventional angiotensin-converting enzyme inhibitors. In this unique case, angioedema was associated with a transient ischemic attack.*
E. J. B.

Rupprecht R, Vente C, Grãfe A, Fuchs T: Angioedema due to losartan. **Allergy** 54:79-82, 1999. ♦♦

Minocycline Use Linked to "Lupuslike" Syndrome

RECENT case reports have suggested a lupuslike syndrome occurring in patients taking minocycline, a tetracycline drug used in acne treatment. A case-control study was performed to assess this relationship. The study cohort consisted of 27,688 patients, aged 15 to 29 years, with acne. Ninety-three percent were female. Twenty-nine cases of lupuslike syndrome were identified, defined by criteria including polyarthritis or polyarthralgia with a positive or unmeasured antinuclear factor and an elevated or unmeasured erythrocyte sedimenation rate. One hundred fifty-two controls were matched to the cases for age, sex, and practice.

Among current tetracycline users, the incidence rate of lupuslike syndrome was approximately 14 cases /100,000 prescriptions. The incidence rate was just 2.3 cases/100,000 prescriptions in males versus 32.7/100,000 in females. Current single use of minocycline carried an odds ratio of 8.5 (95% confidence interval 2.1 to 35) for the development of lupuslike syndrome. This was 3- to 4-fold higher than with other tetracyclines. The larger the cumulative minocycline dose and the longer the duration of treatment, the greater the risk. Risk was unaffected by adjustment for current exposure to oral contraceptives or other potential confounders.

Acne patients taking tetracyclines—especially minocycline—are at increased risk of developing a lupuslike syndrome. Risk is greater in long-term users. This form of drug-induced lupus may result from binding of a reactive metabolite to the class II major histocompatibility antigen, producing an autoimmune reaction.

COMMENT: *The last issue of* ***AllergyWatch*** *presented an interesting series of seven patients with an autoimmune vasculitis. This nested case-control study in a cohort of 27,688 acne patients aged 15 to 29 years showed that current single use of minocycline was associated with an 8.5-fold increased risk of developing a lupuslike syndrome, compared with nonusers and past users. The risk increased with longer use. Since these are common drugs in our patients, allergist/immunologists should be familiar with these potential adverse effects.*
M. S. D.

Sturkenboom MCJM, Meier CT, Jick H, Stricker HC: Minocycline and lupuslike syndrome in acne patients.
Arch Intern Med 159:493-497, 1999. ♦♦

Randomized Trial Finds Echinacea Doesn't Prevent Colds

THIS study evaluated an extract of the Echinacea plant for prevention and treatment of colds and respiratory infections. One hundred nine patients with at least three such illnesses in the previous year were ➤➤

randomized to receive *Echinacea purpurea* extract or placebo, 4 mL twice daily. Over the 8-week treatment period, the incidence and severity of colds and respiratory infections were compared in double-blind fashion.

At least one episode of illness occurred in 65% of the Echinacea group and 74% of the placebo group, a nonsignificant difference. The median duration of illness was also similar between groups: 4.5 and 6.5 days, respectively. The severity of episodes was comparable as well. The Echinacea group had a nonsignificantly higher rate of side effects, 20% versus 13%.

Treatment with Echinacea does not appear to reduce the risk of colds and respiratory infections in patients with a history of frequent illnesses. Neither does it significantly reduce the duration or severity of colds. This randomized trial does not confirm previous reports claiming the clinical efficacy of Echinacea.

COMMENT: *Despite claims by manufacturers and the press on the benefits of Echinacea, its clinical efficacy has never been proven in rigorous, randomized, blinded trials. In this controlled study, treatment with fluid extract of* ***Echinacea purpurea*** *did not decrease the incidence or severity of cold and respiratory infections compared with placebo.*
E. J. B.

Grimm W, Müller H-H: A randomized controlled trial of the effect of fluid extract of ***Echinacea purpurea*** *on the incidence and severity of colds and respiratory infections.* **Am J Med** 106:138-143, 1999. ♦♦

Fluticasone Helps Wean Asthma Patients Off Oral Steroids

INHALED fluticasone propionate powder was studied for its ability to reduce the dosage of oral prednisone in patients with severe asthma without compromising safety. The study included 111 adolescent and adult patients with chronic asthma. All were dependent on oral prednisone, with a daily dosage of 5 to 40 mg; their mean FEV_1 was 61% of predicted. They were randomized to receive 16 weeks of treatment with fluticasone propionate, 500 or 1,000 µg twice daily given by multidose powder inhaler, or placebo. Reduction in oral prednisone dose was attempted under a standard protocol, based on specified asthma stability criteria.

Oral prednisone was completely eliminated in 75% of patients receiving fluticasone 500 µg and 89% of patients receiving fluticasone 1,000 µg, compared with just 9% of patients receiving placebo. Particularly at the 1,000 µg dose, fluticasone improved FEV_1, morning and evening peak expiratory flow, asthma symptoms, albuterol use, and nighttime awakenings. Weaning from oral prednisone was also associated with improvement in hypothalamic-pituitary-adrenal axis suppression. Most of the adverse effects recorded were topical effects of inhaled corticosteroids or symptoms of prednisone withdrawal. Patients taking fluticasone also had significant improvements on quality of life measures.

Inhaled fluticasone propionate powder appears to be highly beneficial for patients with severe, chronic asthma. Fluticasone improves lung function, adrenal function, and quality of life, eliminating the need for oral prednisone in most patients. Fluticasone propionate is a safe and effective alternative for reducing the systemic corticosteroid burden of patients with severe asthma.

COMMENT: *Reducing or eliminating oral steroid use in the patient with severe asthma is a major goal of proper treatment. This study documents inhalational fluticasone as a promising agent in that respect, with 89% of patients taking 1,000 µg twice daily able to stop oral prednisone by 16 weeks. Aggressive treatment with high-dose inhaled corticosteroids in steroid-dependent asthmatics can lead to better asthma control with decreased systemic side effects.*
M. S. B.

Nelson HS, Busse W, deBoisblanc BP, et al: Fluticasone propionate powder: oral corticosteroid sparing effect and improved lung function and quality of life in patients with severe chronic asthma.
J Allergy Clin Immunol 103:267-275, 1999. ♦♦

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