AllergyWatch®

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

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Fexofenadine offers better skin penetration than diphenhydramine

THIS study compared the skin distribution of the newer, nonsedating H_1-antagonist fexofenadine with that of the potentially sedating agent diphenhydramine in healthy volunteers. The two agents were also compared for their onset, extent, and duration of H_1-blockade in the skin.

The researchers recruited seven healthy young men; all were free of skin disease and had light-enough skin for visual assessment of flare responses. On the first study day, the men underwent skin biopsy, venipuncture, and histamine skin testing. There were then randomized to receive 7 days of treatment with fexofenadine 120 mg or diphenhydramine 50 mg. (Molar doses were 2.4 and 1.7 x 10^{-4} mol, respectively.) Skin biopsies, blood tests, and histamine skin testing were repeated several times within the first 24 hours after the first dose, and at 12 hours after the final dose.

Skin penetration was significantly greater with fexofenadine than with diphenhydramine at 6, 9, and 24 hours and after 7 days. Both agents reached their maximum skin/plasma ratios within 24 hours. Wheal-and-flare suppression was significantly greater with fexofenadine at 3, 6, and 9 hours; flare suppression was significantly greater after 7 days. At no time did diphenhydramine have better wheal or flare suppression than fexofenadine.

A relatively low 120 mg/d dose of fexofenadine produces good skin penetration with 24-hour suppression of histamine-induced flares in healthy controls. The results suggest that fexofenadine may be more effective than diphenhydramine for chronic urticaria and other allergic skin disorders. The authors call for a randomized, placebo-controlled clinical trial of these two H_1-receptor antagonists for the treatment of urticaria.

COMMENT: *Dr. Simons once again helps to elucidate the activity of antihistamines. In this well-controlled study, the skin concentrations and wheal-and-flare suppressions of diphenhydramine were significantly less than those of fexofenadine. Although* ➤➤

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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
- 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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there was a difference in dosage in milligrams, the authors assure us that on a molar basis the dosages were equivalent. We await future studies evaluating the end-organ concentrations and skin reactivity of other antihistamines to help determine the optimal therapy for the frustrating problem of urticaria.
S. M. F.
Simons FER, Silver NA, Gu X, Simons KJ: Skin concentrations of H1-receptor antagonists.
J Allergy Clin Immunol 107:526-530, 2001.

Lactobacillus Treatment Reduces Atopy Rate in Infants at Risk

THERE are conflicting data regarding the "hygiene hypothesis" as an explanation for recent increases in atopy. The authors propose that, rather than sporadic infections, specific microbes in the healthy gut microflora may play an important role in preventing atopic disease. The GI microflora may contribute to development of T-helper-1-type immunity, generation of transforming growth factor-β, and production of IgA. *Lactobacillus* GG is a probiotic--a culture of a potentially beneficial gut bacterium--that is safe and effective in the treatment of allergic conditions in young children. This study evaluated the effectiveness of *Lactobacillus* GG in preventing atopic disease in infants at high risk.

The double-blind, randomized trial included 159 pregnant Finnish women with a family history of atopic eczema, allergic rhinitis, or asthma. They were randomized to receive either *Lactobacillus* GG or placebo for 2 to 4 weeks before the expected delivery date. Treatment continued for 6 months after birth, either via breast milk or fed to the infants directly. The children were followed up for the development of atopic eczema through the first 2 years of life.

Treatment started a mean of 26 days before delivery. One hundred thirty-two infants completed the study, 35% of whom developed atopic eczema. Six of these children also developed asthma, while one had allergic rhinitis. The frequency of eczema was 23% in patients receiving *Lactobacillus* GG, compared with 46% in those receiving placebo. The relative risk was 0.51 (95% confidence interval 0.32 to 0.84), while the number needed to treat was 4.5 (2.6 to 15.6).

For infants with a family history of atopic disease, antenatal and postnatal treatment with the probiotic *Lactobacillus* GG may significantly reduce the risk of early atopic disease. The results suggest that certain strains of the healthy gut microflora may have very important physiologic and immunologic effects. More study will be needed to understand the immunomodulatory effects of these potentially beneficial microorganisms.

COMMENT: *As in comedy, the secret of a successful therapeutic strategy may be in the timing. This placebo-controlled study shows that perinatal administration of a Gram-positive probiotic,* Lactobacillus rhamnosus *(*Lactobacillus *GG) halved the subsequent occurrence of atopic eczema in at-risk infants. This is a unique and remarkable finding that, if confirmed in other studies, would represent an important advance in the treatment of other allergic diseases.*
E. J. B.
Kalliomäki M, Salminen S, Arvilommi H, et al: Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial.
Lancet 357:1076-1079, 2001. ♦♦

Patients with Aspirin-induced Asthma Tolerate a COX-2 Inhibitor

ASPIRIN and other nonsteroidal inflammatory drugs (NSAIDs) can trigger asthmatic attacks in some patients with asthma. The bronchoconstrictive effect is thought to be related to the drugs' simultaneous inhibition of cyclo-oxygenase (COX)-1 and COX-2. This study evaluated the safe- ➤➤

ty of rofecoxib--a highly specific COX-2 inhibitor--in patients with aspirin-induced asthma.

The study included 12 patients with aspirin-induced asthma. In each patient, the diagnosis was confirmed by symptoms of bronchial obstruction, a greater than 20% decrease in FEV_1, and an increase in urinary leukotriene E_4 excretion in response to oral aspirin challenge. All patients underwent a double-blind, placebo-controlled, crossover challenge study, including four consecutive days of rofecoxib in doses increasing from 1.25 to 25.0 mg. After a 1-week washout period, patients initially challenged with rofecoxib were crossed-over to placebo, and vice-versa.

None of the patients developed dyspnea or a greater than 20% reduction in FEV_1 during rofecoxib treatment. Neither was there any change in leukotriene E_4 or other metabolites. By comparison, two patients had asthma attacks while taking placebo. When rechallenged in open fashion with rofecoxib 25 mg, at least 2 weeks later, none of the patients had any adverse effects.

A specific COX-2 inhibitor does not appear to trigger asthmatic attacks in patients with aspirin-induced asthma. The findings suggest aspirin-induced asthma attacks are triggered by inhibition of COX-1 only, not COX-2. Rofecoxib may be a safe NSAID for use in this group of patients.

COMMENT: *Nonsteroidal anti-inflammatory drug sensitivity involving acute bronchospasm is thought to stem from pharmacologic inhibition of COX. A difficult therapeutic challenge results when NSAID-sensitive asthmatic patients develop arthritis or some other indication for anti-inflammatory medication. While we should remain cautious in our enthusiasm for prescribing an NSAID to patients with NSAID sensitivity, this study using rofecoxib is very encouraging. Future, larger studies should provide more insight into whether individual COX-2 inhibitors are safe for these patients.*
S. A. T.

Szczeklik A, Nizankowska E, Bochenek G, et al: Safety of a specific COX-2 inhibitor in aspirin-induced asthma.
Clin Exp Allergy 31:219-225, 2001. ♦♦

Fluticasone Beats Montelukast for Initial Treatment of Persistent Asthma

UNDER current guidelines, inhaled corticosteroids are preferred as frontline maintenance therapy for mild to severe persistent asthma. Leukotriene-modifying agents are also useful for maintenance treatment of persistent asthma; few clinical trials have directly compared these two types of agents. This randomized study compared low-dose inhaled fluticasone propionate and oral montelukast as frontline maintenance therapy for persistent asthma.

The study included 553 patients, aged 15 years or older, who had persistent asthma symptoms while taking short-acting β_2-agonists. They were randomized to receive fluticasone, 88 µg bid twice daily, or montelukast 10 mg qd for 24 weeks. Fluticasone produced significantly greater improvement in all measures of airway obstruction. Mean improvement in morning predose FEV_1 was 22.9% with fluticasone, compared to 14.5% with montelukast. Fluticasone was also associated with greater improvement in forced midexpiratory flow, 0.66 vs 0.41 L/sec; forced vital capacity, 0.42 vs 0.29 L; morning peak expiratory flow (PEF), 68.5 vs 34.1 L/min; and evening PEF, 53.9 vs 28.7 L/min. In terms of improvement in FEV_1, the advantage of fluticasone was apparent within 2 weeks, and persisted throughout the study. Physicians rated fluticasone as effective or very effective in 71% of cases, compared to 53% for montelukast. Overall asthma quality-of-life scores were higher in the fluticasone group, with clinically significant differences in the domains of asthma symptoms and emotional function.

Compared with montelukast, low-dose fluticasone propionate is superior as initial maintenance therapy for patients with persistent asthma. Fluticasone offers significantly greater improvement in all spirometric measures of airway obstruction, and in most other efficacy endpoints. The advantages of fluticasone may reflect its broad anti-inflammatory effects.

COMMENT: *Again, corticosteroids have been shown to be superior to leukotriene antagonists for control of asthma. Although this trial was longer than previous head-to-head comparisons, it was still for only 6 months. The baseline mean FEV_1 of 65% suggests that most of these patients had "moderate-persistent" asthma, according to the EPR II classification. Most practitioners would agree that inhaled corticosteroids should be first-line therapy for the patient with moderate persistent asthma. This study does not clarify the use of inhaled corticosteroids vs anti-leukotrienes for the patient with mild persistent asthma*
S. M. F.

Busse W, Raphael GD, Galant S, et al: Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial.
J Allergy Clin Immunol 107:461-468, 2001. ♦♦

Early Pet Exposure and Atopic Risk: Birth Cohort Data

ALTHOUGH exposure to furred pets is a risk factor for atopic diseases, the effects of early exposure to pets remain uncertain. Families with a history of allergy are usually advised not to keep pets; however, recent studies suggest that early exposure to pets may actually reduce the risk of atopy. Most such studies have been retrospective in nature. Data from a large Norwegian birth cohort were used to assess the relationship between early pet exposure and development of atopic disease through the first 4 years of life.

The analysis included 2,531 children from the Oslo Birth Cohort Study, born in 1992-93. Questionnaire responses were used to gather data on early-life pet exposure, parental history of atopy, and a wide range of potential confounders. For a subsample of 502 children, house dust samples were collected for measurement of cat and dog allergen.

About 22% of children in the cohort had pets at home. Those with pet exposure were also more likely to be exposed to environmental tobacco smoke in the ➤➤

home. On logistic regression analysis, adjusting for possible confounders, early pet exposure was not associated with bronchial obstruction during the first 2 years of life. Associations of pet exposure with asthma and allergic rhinitis by age 4 were largely negative too. There was no evidence of a differential effect of pet exposure in children with vs without atopic predisposition. Significant levels of cat and dog allergens were measured even in homes without pets.

The results support previous studies finding a negative association between early exposure to pets and risk of atopic conditions. The major strength of this study is its use of prospectively collected data, reducing the chance of recall bias. Confounding effects seem unlikely, though it is difficult to establish a truly unexposed reference group. Early exposure to pets could have a protective effect, or lifestyle or selection factors may play a role.

COMMENT: *These investigators studied the association between early-life exposure to cats and dogs and atopic disease in a large population-based cohort of 2,531 children born in Oslo. They prospectively collected information on pet-keeping, as well as a number of possible confounders. As with previous studies, the results indicated that exposure to pets (or lifestyle issues associated with pet exposure) reduces risk of developing asthma, allergic rhinitis, or atopic eczema. The authors point out that their findings might also be interpreted by selection for keeping pets. (See* AllergyWatch *Jan/Feb 2001, p. 5, and May/June 2001, p. 4.)*
E. J. B.
Nafstad P, Magnus P, Gaarder PI, Jaakkola JJK: Exposure to pets and atopy-related diseases in the first 4 years of life.
Allergy 56:307-312, 2001.

Many Labs Use Inaccurate Specific-IgE Assays

THIS prospective study compared the results of allergen-specific IgE testing at different laboratories. Six laboratories, using five different specific-IgE assays, participated in the study. Over a 6-week period, the laboratories received specimens from 26 serum samples containing different levels of IgE antibodies to common allergens. A total of 7,813 tests were run. The reported results were tested for concordance using Kendall's W nonparametric statistical test; cutoff values and reproducibility were assessed as well.

Most of the assays used showed a low level of concordance. Concordance was particularly poor around the cutoff region, where most assays showed pronounced variability. Two of the laboratories achieved highly comparable results with a high level of precision using the Pharmacia CAP system. Of the other assays, some were reproducible but not accurate while others had low reproducibility and accuracy.

At some laboratories, the commercial assays used for allergen-specific IgE measurement give inaccurate, unreproducible results. In some cases, these results carry significant potential for misdiagnosis. The findings strengthen previous reports showing that the Pharmacia CAP system is reproducible, quantitative, and accurate.

COMMENT: *In vitro testing for allergen-specific IgE remains controversial in many physicians' opinion. Although the technology has progressed substantially, some methods lack precision and accuracy. Allergists and primary care physicians must be aware of those tests which can provide reliable results. This and other studies have conclusively shown that some laboratories use methods with less than adequate diagnostic reliability.*
A. M.
Szeinbach SL, Barnes JH, Sullivan TJ, Williams PB: Precision and accuracy of commercial laboratories' ability to classify positive and/or negative allergen-specific IgE results.
Ann Allergy Asthma Immunol 86:373-381, 2001. ♦♦

Protective Effects of Anti-inflammatory Medications in the "Real World"

IN research settings, inhaled anti-inflammatory medications significantly improve symptoms and lung function in pediatric asthma patients. However, there are relatively few data on the "real-world" effects of these medications in reducing the need for acute care services. The effects of inhaled anti-inflammatory therapy on the rate of hospitalization and emergency department (ED) visits among children with asthma were studied.

The 1-year population cohort study included children with asthma from three urban U.S. managed-care organizations (MCOs). The children, aged 3 to 15 years, were enrolled in the MCOs over a 12-month period in 1996-97. Pharmacy data were used to assess medications dispensed--39% of children received at least one anti-inflammatory medication during the study year.

During the study period, 1.9% of the children were hospitalized and 6.8% made an ED visit for asthma. Multivariate logistic regression analysis was performed to adjust for age, sex, MCO, and dispensing of reliever medications. Compared with children receiving no controller medications, those receiving cromolyn had an adjusted relative risk (RR) of 0.4 for an ED visit. Other adjusted RRs for ED visits were 0.5 for any inhaled corticosteroid (ICS); and 0.4 for any cromolyn or ICS--ie, any controller medication. Cromolyn dispensing was associated with an adjusted RR of 0.6 for hospitalization. Other adjusted RRs for hospitalization were 0.4 for any ICS and 0.4 for any controller medication. Children with more frequent dispensings of reliever medications were at lower risk of both acute-care outcomes.

For asthmatic children in managed care, inhaled anti-inflammatory medications are associated with a reduced risk of hospitalization or ED visits for asthma. Similar effects are noted for cromolyn and ICS. With reliever dispensing as a surrogate for asthma severity, anti-inflammatory therapy appears protective across a wide range of reliever medication use. Use of acute services is elevated for both children with frequent reliever dispensings and those receiving no therapy. ➤➤

COMMENT: *This study of 11,195 children in three geographically diverse MCOs addressed the impact of asthma controller medications on hospitalization and ED visits for asthma in a 1-year period. Because there was no independent measure of asthma severity, the frequency of reliever medication was used as a surrogate. Both cromolyn and inhaled corticosteroids were associated with a significant protective effect on hospitalization and ED visits.*
J. B.-M.
Adams RJ, Fuhlbrigge A, Finkelstein JA, et al: Impact of inhaled antiinflammatory therapy on hospitalization and emergency department visits for children with asthma. **Pediatrics** 107:706-711, 2001. ♦♦

What Are the Chacteristics of Asthma in the Elderly?

ASTHMA is a common problem in older adults, and one that may be underdiagnosed and undertreated. A group of 80 elderly patients with asthma were studied. Symptoms and pulmonary function measures were assessed to determine the severity of disease. House dust samples were collected to evaluate the associated indoor allergens, and 75 subjects underwent skin testing to common airborne allergens. Juniper's Asthma Quality of Life Questionnaire and the Short Form Health Survey Medical Outcome Questionnaire were administered to assess asthma's impact on quality of life and health status.

The asthmatic subjects were 61 women and 19 men, mean age 73.5 years. Most subjects were white and had at least a high-school education. Sixty-five percent were rated as having moderate to severe persistent asthma. Seventy-five percent of skin-tested subjects had a positive response to at least one allergen, with cat hair being the most frequent positive allergen. High levels of dust mite, cockroach, cat, and dog allergen were detected in the subjects' homes, often high enough to put the subjects at risk of symptoms or sensitization. As asthma severity increased, quality-of-life scores decreased in most domains. There was also a trend toward decreased health status. More than three-fourths of subjects used β_2-agonists on a regular or as-needed basis, and more than two-thirds used inhaled corticosteroids regularly.

Asthma is a common problem in the elderly. Many affected patients had moderate to severe persistent asthma, positive skin-test results, and high allergen levels in the home. More severe asthma has a significant impact on quality of life. The authors urge skin testing in elderly patients with moderate to severe asthma, followed by appropriate medications and allergen-control measures.

COMMENT: *As the demographics of our population change, allergists will be increasingly called upon to evaluate and care for elderly patients. This important article and an accompanying editorial highlight the importance of identifying allergic triggers in the elderly. There is little question that an allergy consultation can directly impact the cause of atopic disease even in the sixth and seventh decades of life. (See* AllergyWatch *May/June 2001, p. 10.)*
A. M.
Huss K, Naumann PL, Mason PJ, et al: Asthma severity, atopic status, allergen exposure, and quality of life in elderly persons.
Ann Allergy Asthma Immunol 86:524-530, 2001. ♦♦

Add-on Salmeterol Permits Reduction, but Not Elimination, of Inhaled Steroid Dose

FOR patients whose asthma is inadequately controlled by inhaled corticosteroids (ICS) alone, adding a long-acting β_2-agonist improves asthma control. There is continued debate as to whether the ICS dose can be reduced or even eliminated after such improvement has occurred. This question was addressed in a National Heart, Lung, and Blood Institute trial.

The randomized, controlled trial included 175 adolescent to adult asthma patients treated at six Asthma Clinical Research Network centers. All patients had persistent asthma that did not respond adequately to 6 weeks of treatment with inhaled triamcinolone acetonide, 400 µg twice daily. All continued on this triamcinolone dosage; patients were then assigned to receive 2 weeks of add-on therapy with salmeterol xinofoate, 42 µg twice daily (154 patients) or placebo (21 patients). Subsequently, all patients in the placebo group and one-half of those in the salmeterol group were assigned to gradually reduce and eliminate triamcinolone. The remaining patients, serving as active controls, continued taking both salmeterol and triamcinolone for 16 weeks.

For patients assigned to reduce their ICS dose, the treatment failure rate was 8.3% after 8 weeks, compared with 2.8% in those who continued on both drugs. The difference was nonsignificant. However, by the end of the triamcinolone-elimination period, patients assigned to this condition were 4-fold more likely to have treatment failure: relative risk 4.3, 95% confidence interval 2.0 to 9.2.

Most patients with persistent asthma who are treated with add-on salmeterol can safely reduce their ICS dose without undue risk of treatment failure. However, the treatment failure rate is unacceptably high when ICS treatment is withdrawn completely.

COMMENT: *This study builds on previous work demonstrating that the addition of long-acting inhaled β-agonist is equal to or more effective than doubling the dose of inhaled corticosteroid in subjects with persistent asthma. The clinical question addressed in this paper is whether the dose of inhaled corticosteroid can safely be reduced or discontinued after stabilization of asthma on the combination of inhaled corticosteroid and long-acting β-agonist. The data support reducing the inhaled corticosteroid to a low dose, but discontinuation results in significant deterioration of asthma control.*
D. K. L.
Lemanske RF Jr, Sorkness CA, Mauger EA, et al: Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial.
JAMA 285:2594-2603, 2001. ♦♦

Depression in mothers of children with asthma linked to increased ED visits

PREVIOUS studies have suggested that mothers with social and behavioral problems are more likely to bring their children to the emergency department (ED) unnecessarily. For children with asthma, having a caregiver with high psychologic distress is a powerful predictor of hospitalization. This study evaluated the relationship between maternal depressive symptoms and ED utilization by inner-city children with asthma.

A depression questionnaire and other measures were administered to the mothers of 140 inner-city children with asthma. Fifty-six percent of the families were on state-sponsored medical assistance. The children's mean age was 8 years, and 59% were girls.

Forty-seven percent of the mothers had clinically significant symptoms of depression. Compared to mothers with low levels of depression, the depressed mothers had a higher unemployment rate, were more likely to be unemployed, and were more likely to be in the lowest income stratum. Most indices of asthma care were similar between the two groups, including lifetime asthma hospitalizations and visits for routine asthma care. However, mothers with high levels of depressive symptoms were 40% more likely to report taking their child to the ED in the past 6 months. Other factors associated with high ED utilization included maternal age 30 to 35 years and more severe asthma morbidity. Even after adjustment for these factors, mothers with high levels of depressive symptoms remained 30% more likely to report recent ED visits.

Nearly half of mothers of inner-city children with asthma have clinically significant depressive symptoms, and these mothers are more likely to bring their children to the ED. The very high rate of depression in these urban mothers itself increases health care utilization. Measures to improve mothers' psychologic adjustment may help to promote better asthma care for their children.

COMMENT: *In this impressively controlled, prospective study, the investigators found an incredibly high (40%) likelihood of ED use in children with asthma whose mothers had symptoms of depression. The sample population was inner-city, but I would assume the findings are applicable to suburban practices. The factors that influence outcomes in asthma care continue to get more complicated. Not only are children influenced by a parent's genetics, but maternal depression can also have negative effects on the child's asthma control.*
S. M. F.

Bartlett SJ, Kolodner K, Butz AM, et al: Maternal depressive symptoms and emergency department use among inner-city children with asthma.
Arch Pediatr Adolesc Med 155:347-353, 2001. ♦♦

Do Psychiatric Conditions Affect Health Care Use in Severe Asthmatics?

PREVIOUS studies have linked certain psychosocial variables in asthma patients to poor disease control, which leads to increased treatment costs. This study assessed the effects of psychiatric disorders on health care utilization among patients with severe asthma.

The study included 98 Dutch adults with severe bronchial asthma. All had persistent symptoms, despite using high doses of inhaled corticosteroids and long-acting bronchodilators. In addition, all had difficult-to-control asthma, associated with a recent course of high-dose oral corticosteroids or maintenance therapy with oral prednisone. Psychiatric "cases" were identified by a score of 6 on the 12-item General Health Questionnaire (GHQ), a screening test for nonpsychotic psychiatric disturbances.

Twenty-one patients were identified as psychiatric cases, with a median GHQ score of 8. They were similar to the 77 "noncases" in terms of demographic variables and asthma characteristics. However, the two groups differed significantly in several measures of health care utilization. The percentage of patients visiting their general practitioner more than four times in the previous year was 71% among the psychiatric cases vs 30% for the noncases. The psychiatric cases were also more likely to have made two or more emergency department visits, 71% vs 31%. Ninety-two percent of the psychiatric cases had experienced at least two asthma exacerbations in the previous year, compared with 57% of the noncases. The percentage of patients with two or more hospitalizations was 19% vs 5%, respectively. With adjustment for age, sex, and FEV_1, the psychiatric patients were 11-fold more likely to have two or more exacerbations and 5-fold more likely to have two or more hospitalizations.

Among patients with severe asthma, health care utilization is substantially higher for those with psychiatric disorders. Much of the morbidity and economic costs attendant on severe asthma may be related to psychologic dysfunction, rather than the severity of disease itself. The benefits of screening for and treating psychopathology in patients with severe asthma remain to be determined.

COMMENT: *It's not surprising to learn that among severe asthmatics, those with evident psychopathology have greater utilization of health care resources and greater risk for life-threatening complications of their disease. The reasons for this may involve differences in symptom perception or adherence to treatment regimens. Of note, while psychopathology might complicate asthma treatment, psychologic disturbances as measured here were no more common among severe asthmatics than in the general population. This report emphasizes the need to screen for psychiatric problems in the evaluation of severe asthmatics in the hope of detecting a treatable disorder.*
J. R. B.

ten Brinke A, Ouwerkerk ME, Zwinderman AH, et al: Psychopathology in patients with severe asthma is associated with increased health care utilization.
Am J Respir Crit Care Med 163:1093-1096, 2001.

Characteristics of Allergic Reactions to Peanut/Tree Nut at School

DATA from the U.S. Peanut and Tree Nut Allergy Registry suggest that, although most initial reactions to these food allergens occur in the home, subsequent exposures are more likely to occur in other settings. A detailed analysis of allergic reactions to peanut and tree nut occurring in school or day care settings is presented.

Of a total of 4,586 persons reporting reactions to the Registry, 750 reported reactions occurring at school or day care. Telephone interviews were conducted with a random sample of 100 subjects or their parents.

Of the total 124 reactions described, 64% occurred at day care or preschool. In one-fourth of cases, a reaction occurring at school was the first evidence of allergy. The route of exposure was ingestion in 60% of episodes, skin contact in 25%, and possible inhalation in 16%. Most of the ingestion reactions involved cookies or other baked products. Craft projects using peanut butter (making bird feeders) were an important source of exposure. The reactions occurred a median of 1 minute after exposure. In most cases, a teacher was the first adult to become aware of the reaction and to take charge of the situation. Medications were given in 90% of episodes, most often antihistamines. One-third of the schools had an emergency plan for handling reactions, but the plan was not followed in about one-fourth of cases.

Teachers and other school personnel require education in the recognition and treatment of nut allergies. Treatment delays may result from failure to recognize a reaction, calling parents rather than giving medication, and inability to administer epinephrine injections. Schools should have a plan for handling such emergencies, including epinephrine injection.

COMMENT: *This study characterizes food allergic reactions in 750 participants of a U.S. registry who had one or more reactions to peanut or tree nut in school or day care. Interestingly, two-thirds of the reactions occurred in preschool or day care. The results strongly support the thesis that school personnel must be educated to recognize signs of allergic reactions, and that schools should have a plan in place to treat symptoms.*
J. B.-M.

Sicherer SH, Furlong TJ, DeSimone J, Sampson HA: The US Peanut and Tree Nut Allergy Registry: characteristics of reactions in schools and day care.
J Pediatr 138:560-565, 2001. ♦♦

Angioedema unmasked by ACE inhibitors: case report

PATIENTS with a deficiency of C1-esterase inhibitor (C1-INH) may experience potentially serious attacks of angioedema involving the tongue, throat, or larynx. A patient with acquired C1-INH deficiency who developed life-threatening angioedema after treatment with an angiotensin-converting enzyme (ACE) inhibitor is reported.

A 71-year-old man was brought to the emergency department with severe facial angioedema with swelling of the face and tongue, stridor and respiratory distress, and laryngeal edema. The attack resolved over 4 days, with little response to epinephrine, antihistamines, or corticosteroids. The patient had previously had only a few mild episodes of angioedema and abdominal pain. Six months before the life-threatening attack, he was put on quinipril, 10 mg/d, for treatment of mild hypertension. Serum protein electrophoresis showed an IgG2 autoantibody directed specifically against C1-INH. Complement activation was demonstrated by the presence of reduced C1-INH, C1q, and C4. The patient had no further serious attacks after stopping ACE inhibitor therapy. His C1-INH level remained low, and his anti-C1-INH antibodies high.

In this patient, ACE inhibition appears to have unmasked an unknown acquired autoimmune C1-INH deficiency, leading to a life-threatening attack of angioedema. Angioedema is a rare but potentially serious complication of ACE inhibitor therapy.

COMMENT: *This unique case report highlights the important role of ACE inhibitors in the induction of allergic responses. Clinicians should be cautious of administering ACE inhibitors to patients who have previously experienced angioedema.*
A. M.

Kleiner GI, Giclas P, Stadtmauer G, Cunningham-Rundles C: Unmasking of acquired autoimmune C1-inhibitor deficiency by an angiotensin-converting enzyme inhibitor.
Ann Allergy Asthma Immunol 86:461-464, 2001. ♦♦

Mycobacterial Antigen Yields Improvement in Atopic Dermatitis

THE rising prevalence of atopic dermatitis and other diseases in Western societies has occurred at a time of dramatic reductions in infectious disease, particularly tuberculosis. This raises the possibility that reduced exposure to mycobacterial antigens may be a causal factor in the increasing frequency of atopy. This study evaluated the effects of immunization with a mycobacterial antigen in children with atopic dermatitis.

The randomized, placebo-controlled trial included 41 children and adolescents with moderate to severe atopic dermatitis. The patients received a single intradermal injection of killed *Mycobacterium vaccae* (SRL 172) or buffer solution. At 1 and 3 months, the change in skin surface area involved by dermatitis and the dermatitis severity score were assessed.

Mean reduction in surface area affected by dermatitis was 48% in children receiving SRL 172, compared with only 4% in those receiving buffer solution. Dermatitis severity score decreased by a median of 68% and 18%, respectively. There were no serious adverse effects of SRL 172.

Treatment with a killed *Mycobacterium* suspension is associated with significant clinical improvements in children with atopic dermatitis. The findings ➤➤

are consistent with previous studies showing an inverse relationship between tuberculin responses and atopic diseases. Treatment with mycobacterial antigens could be a simple adjuvant to conventional topical steroid therapy for patients with atopic dermatitis.

COMMENT: *One of the intriguing theories about the increasing prevalence of atopic diseases is the "hygiene hypothesis": reduced microbial exposures in the Western, urban world may convert us to a population of Th2-predominant, allergy-prone folks. In this study, 41 children with moderate to severe atopic dermatitis were given either a single intradermal dose of killed* M. vaccae *or placebo, then followed up for 3 months. The improvements in dermatitis surface area and severity score were impressively greater in the vaccinated group. The ultimate duration of the response is unknown. It's curious how some microbes seem to provide superantigens, while others are immunosuppressant. Mars and Venus all over again?*
R. J. M.
Arkwright PD, David TJ: Intradermal administration of a killed Mycobacterium vaccae *suspension (SRL 172) is associated with improvement in atopic dermatitis in children with moderate-to-severe disease.*
J Allergy Clin Immunol 107:531-534, 2001. ♦♦

IV Theophylline Benefits Children with Status Asthmaticus

METHYLXANTHINE drugs such as theophylline have significant benefits in acute episodes of bronchial obstruction and are safe in therapeutic doses. The role of combination therapy with methylxanthines and β-agonists in patients with severe status asthmaticus remains unclear. This study evaluated the effects of adding theophylline to modern drug treatment for severe status asthmaticus in children.

The randomized, controlled trial included 47 children, median age 8.3 years, admitted to a pediatric ICU with severe status asthmaticus. All patients received aggressive medical therapy, including inhaled and IV β-agonists, inhaled ipratropium, and IV methylprednisolone. In addition, one group of children received IV theophylline infusions to achieve a serum drug level of 12 to 17 μg/mL. The response was measured in terms of clinical asthma score.

Children assigned to the theophylline group received their complete loading dose within 2.1 hours after arriving in the ICU. The two groups were similar in their baseline asthma scores; 3 patients in each group received mechanical ventilation. Among nonventilated children, mean time to reach a clinical asthma score of 3 or less was 18.6 hours in the theophylline group, compared with 31.1 hours in the control group. Theophylline did not appear to alter the need for continuous inhaled albuterol or IV terbutaline. Children receiving theophylline had a larger reduction in baseline respiratory rate., but no difference in length of ICU stay or total incidence of side effects.

For children with severe status asthmaticus, adding theophylline to standard β-agonist, anticholinergic, and steroid therapy appears to shorten time to recovery. The study finds no difference in length of ICU or hospital stay among children receiving theophylline. Further study is needed to clarify the mechanism of action of methylxanthine drugs, and their interactions with β-agonists and other drugs.

COMMENT: *Many of us have been waiting for the pendulum to swing back toward the routine use of theophylline in the acute or chronic management of asthma. Conducted in a pediatric ICU setting, the subjects in this study all received continuous inhaled albuterol, intermittent inhaled ipratropium, and systemic corticosteroids. Despite these "state-of-the-art" interventions, the subjects who also received intravenous theophylline shortened their recovery time by 40%.*
S. A. T.
Ream RS, Loftis LL, Albers GM, et al: Efficacy of IV theophylline in children with severe status asthmaticus.
Chest 119:1480-1488, 2001. ♦♦

Two Years of Inhaled Steroids Doesn't Reduce Bone Density in Mild Asthmatics

THE risk-benefit ratio of inhaled steroids for patients with mild asthma remains unclear. This randomized trial evaluated the effects of 2 years of inhaled corticosteroid therapy on bone mineral density in adult patients with mild asthma.

The multicenter, international study included 374 patients, mean age 35 years, with mild asthma treated with β-agonists only. The patients were randomized into three treatment groups: inhaled budesonide, inhaled beclomethasone dipropionate, or nonsteroid treatment. Each treatment continued for 2 years; in the corticosteroid groups, dose adjustments were made based on asthma severity and treatment response. Although treatment assignment was "open," follow-up measurements of bone mineral density--performed at 6, 12, and 24 months--were made in blinded fashion.

Two hundred thirty-nine patients completed the study. The budesonide group received a median daily dose of 389 μg, and the beclomethasone group a dose of 499 μg. Inhaled corticosteroids achieved better asthma control, although symptoms and β-agonist use decreased in all three groups. There were no differences in the 2-year change in bone mineral density among groups, and the changes that did occur were unrelated to changes in bone metabolic markers. There was a significant correlation between inhaled steroid dose and bone mineral density at the lumbar spine, but not at the femoral neck.

In adult patients with mild asthma, 2 years of treatment with inhaled corticosteroids produces little change in bone mineral density. Inhaled steroids also provide better asthma control than alternative, nonsteroid therapies. The inhaled corticosteroid dose is related to change in bone density at the lumbar spine and inversely related to lung function; the current study cannot rule out the possibility that asthma severity affects bone density.

COMMENT: *There are many studies addressing this important issue. Unfortunately, there are many differences in the approaches used, making comparisons* ➤➤

difficult. This study in 239 patients with mild asthma shows that treatment with an inhaled corticosteroid provides better asthma control than the alternative treatment chosen by the attending physician. As well, there was no difference in mean change in bone mineral density between three groups of patients (inhaled budesonide vs inhaled beclomethasone dipropionate vs nonsteroid treatment) after 2 years. (See AllergyWatch *July/Aug 2000, p. 1.)*
E. J. B.
Tattersfield AE, Town GI, Johnell O, et al: Bone mineral density in subjects with mild asthma randomised to treatment with inhaled corticosteroids or non-corticosteroid treatment for two years.
Thorax 56:272-278, 2001. ♦♦

Asthma Linked to Chronic *Chlamydia* Infection

SEVERAL lines of evidence suggest that respiratory infectious organisms--including the intracellular pathogen *Chlamydia pneumoniae*--may play a causative role in asthma. This serologic study examined the prevalence of antibodies to *C. pneumoniae* in asthma patients vs controls.

A microimmunofluorescence test for *C. pneumoniae*-specific IgG, IgM, and IgA antibodies was performed in serum samples from 33 adult asthma patients and the same number of matched controls. Twenty-four of these asthma patients had longstanding disease, while the other 9 were recently diagnosed.

The rate of *C. pneumoniae*-specific IgG antibodies--indicating past infection--was 64% in the asthma patients and 58% in controls. Eighteen percent of the asthma patients had high titers of IgG antibodies (1:512 or greater), compared with 3% of controls. The rate of high IgA titers (1:40 or greater) was significantly different between groups: 52% in the asthma patients vs 15% in controls. This rate did not differ between the chronic and recently diagnosed asthma patients. The combination of high-titer IgG and high-titer IgA--indicating chronic *C. pneumoniae* infection--was found in 18% of asthma patients vs 3% of controls.

Asthma patients are more likely to show serologic evidence of chronic *C. pneumoniae* infection than controls. The study permits no conclusions about whether this respiratory pathogen is a causative factor in the development of asthma. More likely, *C. pneumoniae* infection is related to a certain type of asthma.

COMMENT: *These asthma patients had no detectable IgM to* Chlamydia. *However, significantly more asthmatics than controls had high levels of anti-*Chlamydia *IgA and IgG, indicative of chronic infection. This was true of patients with both recent onset of untreated asthma and chronic well-controlled asthma. The question remains as to whether* Chlamydia *infection is the cause of asthma or whether asthmatics are in some way predisposed to chronic* Chlamydia *infection. The therapeutic implications are uncertain; however, several studies have shown improvement in asthma control with the use of macrolide antibiotics.*
J. R. B.
Gencay M, Rüdiger JJ, Tamm M, et al: Increased frequency of Chlamydia pneumoniae *antibodies in patients with asthma.*
Am J Respir Crit Care Med 163:1097-1100, 2001. ♦♦

High Rate of *Mycoplasma* and *Chlamydia* in Patients with Chronic, Stable Asthma

In a previous study, the authors found evidence of *Mycoplasma pneumoniae* in the airways of 10 of 18 patients with chronic, stable asthma. Other studies have suggested that *Chlamydia pneumoniae* may also be associated with chronic asthma. Evidence of these two respiratory pathogens was sought in a larger population of patients with chronic, stable asthma.

The investigators recruited 55 subjects with chronic stable asthma, each with a methacholine PC_{20} of less than 8 mg/mL and reversibility of lung function by at least 15% with bronchodilator. Eleven subjects without evidence of atopy or bronchial hyperresponsiveness were studied as controls. Culture, polymerase chain reaction (PCR), and serologic studies for *Mycoplasma* and *Chlamydia* species and respiratory viruses were performed, and the bronchoalveolar lavage cell count and differential and tissue morphometric findings were assessed.

On PCR, 45% of asthmatic subjects were positive for *Mycoplasma* species--mainly *M. pneumoniae*--compared with just 9% of controls. The rate of PCR positivity for *C. pneumoniae* was 13% for asthmatic subjects vs zero for controls. Overall, 56% of the asthma group were positive for *Mycoplasma* and/or *Chlamydia* species. The rate of PCR positivity was 39% for asthmatic patients taking inhaled corticosteroids (ICS) vs 65% for those not taking ICS. In airway biopsies, the PCR-positive patients had significantly greater mast cell infiltration and a trend toward higher numbers of T lymphocytes. Rates of respiratory virus detection were similar for asthmatic subjects and controls.

Chronic, stable asthma is associated with the presence of *Mycoplasma* and/or *Chlamydia* species in the airways, as demonstrated by PCR. The findings strengthen the theorized relationship between chronic infection and chronic asthma. Patients with positive PCR results have increased mast cell numbers.

COMMENT: *These researchers expand their previous report from 2 years ago in which they detected* Mycoplasma *in the airways of chronic asthmatics. In the new study, they found that 56% of chronic asthmatics had evidence of infection with either* Mycoplasma *or* Chlamydia, *compared with only 1 of 11 patients in the normal control group. It was of interest that treatment with ICS influenced the rate of positive PCR results. Only 18 of the 55 asthmatic patients were receiving ICS, and twice as many patients on ICS had negative PCR results. Could the use of ICS influence the presence of micro-organisms from the airways in asthmatics?*
S. M. F.
Martin RJ, Kraft M, Chu HW, et al: A link between chronic asthma and chronic infection.
J Allergy Clin Immunol 107:L595-601, 2001. ♦♦

Can Atopy Patch Testing Avoid the Need for Food Challenges?

DIAGNOSTIC evaluation for patients with suspected food allergy includes skin prick tests and measurement of specific IgE. Recent studies have suggested that atopy patch tests (APTs) may be useful as well. This study evaluated the effects of combining these allergologic tests, with the goal of avoiding double-blind, placebo-controlled food challenges (DBPCFCs).

The analysis included a total of 173 oral provocation tests performed in 98 consecutive children with atopic dermatitis and suspected food allergies. Forty-one percent of the patients were challenged with cow's milk, 24% with hen's egg, 20% with wheat, and 15% with soy. Each child also underwent SPTs, APTs, and specific IgE measurement. The study hypothesis was that some combination of the latter tests would predict the presence of food allergy with a positive predictive value (PPV) of greater than 90%, thus obviating the need for DBPCFC.

Fifty-five percent of the oral provocation tests were positive. The best predictor of allergy to cow's milk was the APT, with a PPV of 95%. Combining a positive APT with a positive SPT or specific IgE raised the PPV to 100%. For hen's egg allergy, the APT offered a PPV of 94%--in this case, combining the results of other tests did not improve diagnostic performance. The level of specific IgE was a strong predictor of the results of oral challenge with both milk and egg. For wheat allergy, the APT had a PPV of 94%, which was not improved by combination with other tests.

The results support the value of APT in children with atopic dermatitis and suspected food allergy. When allergy to cow's milk or hen's egg is suspected, the combination of a positive APT with measurement of specific IgE levels obviates the need for DBPCFC. Relevant specific IgE values are 0.35 kU/L or greater for cow's milk and 17.5 kU/L or greater for hen's egg.

COMMENT: *Diagnosing food allergies by DBPCFC, the "gold standard," is fraught with problems, including danger (anaphylaxis), logistics, and expense. There may be an alternative, at least for some foods. These authors studied children with atopic dermatitis and challenge-proven food allergies to cow's milk, eggs, and wheat. They compared the results of 72-hour patch tests, supplemented with prick test or specific IgE level, with those of DBPCFC. The PPV of each of the three patch tests was 94% to 95%. Considering also the prick or in vitro test result improved the PPV for milk to 100%, but did not improve the other two. The patch test was less sensitive but more specific than the prick or on vitro tests for milk and egg, but more sensitive and specific for wheat. The authors don't clarify what type of immunologic reaction is being observed by the patch test, but the PPV is impressive in their hands. These results probably should not be extrapolated to other antigens.*

R. J. M.

Roehr CC, Reibel S, Ziegert M, et al: Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis.
J Allergy Clin Immunol 107:548-553, 2001. ♦♦

Montelukast vs Salmeterol as Second-Line Therapy for Persistent Asthma

MANY asthma patients with an inadequate response to inhaled corticosteroids receive long-acting β_2-agonists as second-line therapy. However, there is concern that β_2-agonists, as bronchodilators, may mask underlying inflammation. This study compared the bronchoprotective effects of salmeterol and montelukast as second-line therapy for patients with an inadequate response to inhaled corticosteroids.

The study included 20 adult patients with moderate persistent asthma. In crossover fashion, they received 2 weeks of treatment each with montelukast, 10 mg once daily, and salmeterol, 50 µg bid. Montelukast was accompanied by placebo inhaler and salmeterol by placebo tablet. The patients also received placebo during 1-week run-in and washout periods. The main study end point was the bronchoprotective effect against adenosine monophosphate (AMP) challenge.

From the first dose, salmeterol was associated with significant improvement in all lung function parameters, After 2 weeks, both second-line drugs were associated with significant improvement in rescue bronchodilator requirement and peak expiratory flow. Montelukast was associated with suppression of the eosinophil count, which salmeterol was not. For the main outcome measure of bronchoprotection in response to AMP challenge, montelukast had a significant effect after 2 weeks, but salmeterol did not.

Both montelukast and salmeterol can significantly improve asthma control when given as second-line therapy. In addition, montelukast appears to have significant anti-inflammatory effects, reflected by bronchoprotection against AMP challenge and eosinophil suppression. A longer treatment period may be required to realize the maximal effect of montelukast.

COMMENT: *The strengths of this small head-to-head trial are that it was not industry sponsored and it used bronchoprovocation as its primary endpoint. Its weaknesses include its short duration and lack of double-blind design. The results add to the growing literature supporting long-acting β-agonists as the more potent bronchodilators. Leukotriene modifiers are anti-inflammatory and less likely to result in bronchoprotective tolerance.*

S. A. T.

Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ: Evaluation of salmeterol or montelukast as second-line therapy for asthma not controlled with inhaled corticosteroids. **Chest** 119:1021-1026, 2001. ♦♦

Severe Allergic Reactions to Food by Noningestant Contact: 5 Cases

ALLERGIC reactions to food usually follow ingestion, but sometimes can occur after skin contact or inhalation. Five children with severe allergic reac- ➤➤

tions to food caused by skin contact are described.

The patients were 4 boys and 1 girl. Each had severe allergic reactions--including anaphylaxis in 3 patients--following apparently trivial skin contact with cow's milk or peanut. For example, one infant developed urticaria when his mother kissed him after eating cereal with milk. In 1 case, symptoms of wheezing occurred after inhalation contact (with peanut and shrimp). All of the children had a strong positive family history of allergy. In each case, the initial reactions occurred in infancy while the children were being breast-fed--in 4 cases, breast-fed exclusively. Serum total IgE levels were very high, 61 to 1,270 IU/mL. All of the children had strong positive reactions to foods by skin prick or radioallergosorbent testing. The children also reacted to a wide range of ingested foods, most commonly milk, egg, and peanut.

These children had severe reactions to skin contact or inhalation of tiny amounts of food allergen. These patients may be characterized by high serum total IgE, strong family history of allergy, early onset of allergies despite breast-feeding, and strong reactivity on testing. Management for such exquisitely food-sensitive children must include scrupulous allergen avoidance and appropriate emergency medications.

COMMENT: *These case reports serve as an important reminder that food allergy is an important clinical condition in young children. Despite being breast-fed, all 5 children experienced severe allergic reactions to milk and/or peanut by cutaneous or inhalant exposures.*
A. M.

Tan BM, Sher MR, Good RA, Bahna SL: Severe food allergies by skin contact.
Ann Allerg Asthma & Immunol 86:583-586, 2001. ♦♦

Specific immunotherapy for dust-mite allergy: 3-year results

PREVIOUS studies have suggested that specific immunotherapy (SIT) may reduce allergic inflammation and bronchial hyperreactivity (BHR) for patients allergic to pollen, cat, and house-dust mite. This 3-year study evaluated the long-term effects of SIT in dust-mite-allergic patients, including symptom scores and nonspecific BHR.

The study included 27 patients who completed a randomized, double-blind trial of SIT for house dust mite allergy. Each had symptoms of perennial rhinitis and/or mild asthma. Sixteen patients, assigned to active treatment, continued on 8-weekly maintenance SIT for 3 years; the other 11, assigned to the placebo group, started active SIT after a treatment-free interval of 6 months. The patients followed a clustered SIT regimen, consisting of two to three injections at 30-minute intervals until reaching the maintenance dose. Treatment outcomes, evaluated yearly, included rhinitis and asthma scores, specific skin and conjunctival tests, methacholine BHR testing, and medication use.

At the end of 1 year of SIT, all outcome measures showed significant improvement. Furthermore, all measures showed additional improvement at the 2- and 3-year analyses. This included significant reductions in allergen-specific skin and conjunctival reactivity, improvement in methacholine-induced BHR, and reduced use of medications for asthma and rhinitis. There was no change in Der p-specific circulating IgE levels.

Patients with house-dust-mite allergy show significant and continued improvement over 3 years of SIT. This study documents reductions in symptom scores, medication use, and nonspecific BHR. The results strengthen the argument for "early" SIT in patients with allergic rhinitis and asthma.

COMMENT: *This well-controlled study evaluated a standardized house dust extract in 27 patients over a 3-year period. All patients improved within 12 months of study and continued to improve over the next 2 years. Rhinitis and asthma symptom scores improved as well as reactivity to skin and conjunctival provocation. Bronchial hyperreactivity was also reduced. Clinically, the results facilitated reduction of medication. These encouraging results need to be studied further in patients with more severe disease.*
E. J. B.

Pichler CE, Helbling A, Pichler WJ: Three years of specific immunotherapy with house-dust-mite extracts in patients with rhinitis and asthma: significant improvement of allergen-specific parameters and of nonspecific bronchial hyperreactivity. **Allergy** 56:301-306, 2001.♦♦

Antibody to Trimellitic Anhydride Detects Binding to Lung Epithelial Cells

THE low-molecular-weight, highly reactive acid anhydrides--widely used in the paint and plastics industries--have been linked to various occupational lung diseases, including asthma and pneumonitis. Studies in rats have shown that the inhaled vapor of trimellitic anhydride (TMA) binds to alveolar and bronchial cells, but there is currently no reagent for use in identifying the primary target proteins for TMA binding.

The authors describe the development of an antibody to TMA for use in in vitro studies of TMA binding to lung epithelial proteins. The monoclonal antibody, designated HSE 7, binds solely to TMA and can be inhibited only by TMA or TMA conjugate. This is so regardless of the carrier molecule used, underscoring the importance of TMA in forming the epitope for the antibody. When used to probe a western blot of A549 lung epithelial cells exposed to TMA, HSE 7 detected 10 bands in the molecular weight range of 20 to 30 kD.

The HSE 7 monoclonal antibody is a sensitive and specific reagent for detection of protein-bound TMA. When lung epithelial cells are incubated with TMA, it binds to proteins within a restricted range of molecular weights. The findings question current approaches for detecting IgE to small-molecular-weight reactive chemicals, which assume that the chemicals bind to serum albumin. The potential for cell damage resulting from TMA binding to lung epithelial cell proteins is uncertain.

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COMMENT: *Objective confirmation of sensitization to occupational allergens is often problematic, partly because of poor sensitivity of antibodies used to detect small-molecular-weight antigens. The monoclonal antibody described in this study appears to have a greater sensitivity for detecting TMA than previously available reagents. It should help in exploring mechanisms of TMA-induced occupational disease and may become a valuable diagnostic tool.*
S. A. T.

Griffin P, Allan L, Beckett P, et al: The development of an antibody to trimellitic anhydride.
Clin Exp Allergy 31:453-457, 2001. ♦♦

REVIEWS OF NOTE

Benson M, Adner M, Cardell LO: Cytokines and cytokine receptors in allergic rhinitis: how do they relate to the Th2 hypothesis in allergy?
Clin Exp Allergy 31:361-367, 2001.

COMMENT: *This review from Sweden provides a nice overview of the Th2 hypothesis as it relates to allergic rhinitis. The authors emphasize the fact that the process is multidirectional and involves "Th2" cytokine expression from sources other than Th-2 cells.*
S. A. T.

Settipane RA, Lieberman P: Update on nonallergic rhinitis.
Ann Allergy Asthma Immunol 86:494-508, 2001.

COMMENT: *The literature on rhinitis is overwhelmingly devoted to allergic disease and allergic models. The reality is that care of nonallergic disease is a major component of the practice of allergy and immunology. This review is a welcome, well-referenced summary of nonallergic rhinitis. The paper's focus is epidemiology, differential diagnosis, and therapeutic options, with less detail on pathophysiology.*
D. K. L.

Brehler R, Kütting B: Natural rubber latex allergy: A problem of interdisciplinary concern in medicine.
Arch Intern Med 161:1057-1064, 2001.

COMMENT: *This succinct review explores the current state of knowledge relating to latex allergy. It also covers some of the more important legislative and economic issues.*
E. J. B.

Kamradt T, Mitchison NA: Tolerance and autoimmunity. **N Engl J Med** 344:655-664, 2001.

COMMENT: *Immunologic tolerance is the process that renders healthy individuals nonreactive to self-antigens. The failure of self-tolerance leads to autoimmune diseases of various kinds. Although there are hundreds of therapies to prevent induction of autoimmune disease in animals, reversing* established *autoimmune disease (established failure of tolerance) is quite another matter. Interferon-β and modulators of interleukin-10 and tumor necrosis factor-α have been used to treat various humans diseases (multiple sclerosis, Crohn's disease, rheumatoid arthritis, and others), with promising but incomplete results. This brief review of tolerance allows one to dream of many more avenues to pursue.*
R. J. M.

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