AllergyWatch®

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

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Pharmacologic Study Supports Fexofenadine and Loratadine for Allergic Skin Disorders

ALTHOUGH H_1-antihistamines have been used for decades in the treatment of allergic skin disorders, there are few comparative data on their clinical pharmacology. Fexofenadine and loratadine are popular examples of the new nonsedating H_1-antihistamines. The clinical pharmacology of these agents in the treatment of allergic skin disorders was studied, including comparison with the sedating H_1-antihistamine chlorpheniramine.

The randomized, double-blind study included 21 healthy young men with no history of skin diseases. They received either 180 mg of fexofenadine, 10 mg of loratadine, or 8 mg of chlorpheniramine. Before the subjects received their assigned drug and at scheduled times from 1 to 24 hours afterward, drug concentrations were measured in plasma samples and skin biopsy specimens. Histamine skin testing was performed as well. Treatment continued for a total of 7 daily doses, with the same assessments performed at 12 to 60 hours after the last dose.

In the fexofenadine group, mean skin concentrations exceeded mean plasma concentrations at all times after the initial dose and at steady state. The ratio of skin to plasma fexofenadine concentration ranged from 1.2 at 1 hour to 110 at 24 hours. Fexofenadine also produced significant suppression of skin wheals and flares in response to histamine. Wheal suppression peaked at 68% and flare suppression at 90% at 3, 6, and 9 hours after the first dose and at 12 hours after the last dose.

Plasma loratadine levels were similar to those reported in previous studies, although few concurrent skin and plasma samples were available in this group. With loratadine, wheal suppression peaked at 66% at 9 hours after the first dose. With chlorpheniramine, wheal suppression peaked at 46% at 3 hours after the first dose while flare suppression peaked at 51% 12 hours after the last dose. ➤➤

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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 Pediatrics
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal

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Fexofenadine concentrations in skin ranged from 400 to 600 ng/g--much higher than chlorpheniramine concentrations. At 36 hours after the last dose, wheal suppression was significantly greater with loratadine than with fexofenadine. Compared with chlorpheniramine, loratadine offered better wheal suppression at 9 hours after the first dose and better flare suppression at 24 hours after the first dose and 36 hours after the last dose. Chlorpheniramine never produced better wheal or flare suppression than either of the two newer antihistamines.

This comparative clinical pharmacology study supports the use of the newer H_1-antihistamines fexofenadine and loratadine for the treatment of allergic skin disorders. Skin distribution of fexofenadine into the skin is 10 times greater than either loratadine or chlorpheniramine; both of the newer agents offer better peripheral H_1 activity than chlorpheniramine. With the availability of these new agents, the use of chlorpheniramine for allergic skin disorders may need to be re-evaluated.

COMMENT: *This investigation evaluated the pharmacology of first- and second-generation antihistamines. Fexofenadine appeared to have a more rapid onset of wheal suppression, but loratadine was better after 5 days of daily dosing. Both were better than chlorpheniramine. Levels of metabolites, such as desloratadine, were not evaluated. There appeared to be some discrepancy between the efficacies of wheal suppression at steady state between the three drugs. Although chlorpheniramine was inferior to both fexofenadine and loratadine, the reduction in wheal suppression for fexofenadine after 5 days was unexplained. Dr. Simons once again uses this wonderful model to further our understanding of antihistamine pharmacology. S. M. F.*

Simons FER, Silver NA, Gu X, Simons KJ, et al: Clinical pharmacology of H_1-antihistamines in the skin.
J Allergy Clin Immunol 110:777-783. ♦♦

Aspirin Sensitivity Linked to Increased CysLT$_1$ Receptor Expression

SOME patients have a well-described idiosyncratic reaction consisting of aspirin sensitivity, asthma, and nasal polyps. Aspirin-sensitive asthma is associated with increased production of cysteinyl leukotrienes and increased airway responsiveness to inhaled cysteinyl leukotrienes, compared with aspirin-tolerant subjects. Aspirin desensitization can be achieved using increasing doses of oral aspirin or topical administration of soluble lysine aspirin. Patients with aspirin sensitivity were studied to determine expression of the cysteinyl leukotriene receptor $CysLT_1$ in nasal biopsy specimens, including the effects of aspirin desensitization.

Two groups of patients with chronic rhinosinusitis and nasal polyposis were studied: 22 with aspirin sensitivity and 12 without. Nasal biopsy specimens were obtained to measure expression of the CysLT1 and LTB_4 receptors. In the aspirin-sensitive group, additional specimens were obtained after topical aspirin desensitization therapy.

The two groups had similar numbers of CD45+ leukocytes in the nasal submucosa. However, total number of cells expressing the $CysLT_1$ receptor was significantly higher in the aspirin-sensitive group: median 542 cells/mm^3, compared with 116 cells/mm^3 in the non-aspirin-sensitive patients. The two groups were similar in expression of $CysLT_1$ or LTB_4 by macrophages, T cells, eosinophils, and mast cells.

The aspirin-sensitive patients received 2 weeks or 6 months of topical lysine aspirin or placebo; very few mild reactions and no severe reactions occurred. With successful desensitization, the numbers of inflammatory cells expressing $CysLT_1$ decreased significantly.

Among patients with chronic rhinosinusitis, those with aspirin sensitivity show increased numbers of inflammatory cells expressing the $CysLT_1$ receptor. The increased expression of the $CysLT_1$ receptor most likely does ➤➤

not explain the increased production of cysteinyl leukotriene noted in these patients. The clinical efficacy of desensitization to aspirin may be related to decreased leukocyte expression of the $CysLT_1$ receptor.

COMMENT: *In aspirin-sensitive patients with asthma and nasal polyps, there may be more than one mechanism for the unusual sensitivity. It is thought that there is overproduction of proinflammatory cysteinyl leukotrienes. Now there is evidence that $CysLT_1$ receptors are overexpressed on inflammatory cells in the respiratory mucosa of these patients. More importantly, aspirin desensitization is shown to diminish respiratory expression. This may account for the beneficial clinical effects of aspirin desensitization.*
R. J. M.

Sousa AR, Parikh AP, Scadding G, et al: Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis.
N Engl J Med 347:1493-1499, 2002. ♦♦

Cardioselective β-Blockers Are Safe in Reactive Airway Disease

PATIENTS with reactive airway disease commonly have coexisting indications for β-blocker therapy, such as hypertension or cardiac arrhythmias. There have been reports of acute bronchospasm occurring in patients taking noncardioselective β-blockers. The cardioselective β-blockers, or β_1 blockers, may lower this risk. The authors performed a meta-analysis to assess the respiratory effects of cardioselective β-blockers in patients with reactive airway disease.

A literature review was performed to identify randomized, blinded, placebo-controlled trials of cardioselective β-blocker treatment in patients with reactive airway disease. Outcomes of interest included FEV_1, symptoms, and use of inhaled β_2-agonists after treatment. Twenty-nine relevant trials were identified: 19 of single-dose treatment (240 patients) and 10 of continued treatment (141 patients).

The data on single-dose treatment suggested a 7.46% decrease in FEV_1, compared with placebo. A single dose of cardioselective β-blocker increased the FEV_1 response to β-agonist treatment by 4.63%, with no increase in symptoms.

In the studies of continued treatment, cardioselective β-blockers were given for 3 days to 4 weeks. The data showed no change in FEV_1, symptoms, or need for inhaled medications compared with placebo. However, cardioselective β-blocker treatment was associated with an 8.74% increase in responsiveness to β-agonists. Studies of patients with concomitant chronic obstructive pulmonary disease showed no effect on FEV_1, whether in response to single doses or continued treatment.

This analysis of previous studies suggests that cardioselective β-blockers have no clinically significant adverse respiratory effects in patients with mild to moderate reactive airway disease. These medications also appear safe for use in patients with chronic obstructive pulmonary disease. Cardioselective β-blockers are of proven efficacy in conditions such as hypertension and heart failure, and should not be withheld because of the presence of reactive airway disease.

COMMENT: *Although the results of this meta-analysis are surprising to me, a few points should be kept in mind. First, most subjects had only mild to moderate airway obstruction and no exacerbations in proximity to study entry. Second, most of the data were from relatively short-term studies and therefore severity of exacerbations may be underestimated. Third, almost 80% of the subjects in the meta-analysis are men, which does not reflect the population of adult asthma. Last, most of the studies showed the group with β -blocker therapy to have a nonstatistical decrease in airway function. It is likely that select individuals may experience clinically significant reduction in lung function even though no statistical difference in the data was found. Nevertheless, this information supports the judicious use of selective β -blocker therapy, such as atenolol or metoprolol, in patients with stable asthma.*
D. K. L.

Salpeter SR, Ormiston TM, Salpeter EE: Cardioselective β-blockers in patients with reactive airway disease: a meta-analysis.
Ann Intern Med 137:715-725, 2002. ♦♦

New Insights into Aspirin-Induced Respiratory Disease

LEUKOTRIENES appear to play a role in the pathogenesis of respiratory reactions to aspirin (ASA) and other nonsteroidal anti-inflammatory drugs. As such, leukotriene-modifier drugs (LTMDs) might be useful in blocking these reactions. The effects of LTMD treatment on ASA-induced lower respiratory tract reactions were evaluated.

The patients were drawn from a series of 271 patients referred to a clinical research center for suspected aspirin-exacerbated respiratory disease. All underwent standard oral ASA challenges. At the time, 96 patients were taking cys-leukotriene receptor antagonists and 12 were taking zileuton. The remaining 163 patients were not taking any LTMDs, although they were receiving topical and sometimes systemic corticosteroids. Responses to ASA challenge were compared between groups, including the prevalence of classic, pure-lower, partial asthma, and upper-only reactions.

The patients who were and were not taking LTMDs were similar in their clinical characteristics and disease severity markers. Most patients had a history of one or more severe asthmatic reactions to ASA or other nonsteroidal anti-inflammatory drugs. Patients receiving cys-leukotriene receptor antagonists were significantly less likely to have bronchospastic reactions to ASA, but more likely to have upper respiratory reactions. For all bronchospastic reactions, the mean percentage decline in FEV_1 was 24.8 in patients receiving cys-leukotriene receptor antagonists and 24.6 in controls. Mean provocative dose of ASA was 60.4 and 70.3 mg, respectively. The percentage of patients with no reaction ➤➤

to ASA was 16% in the zileuton group, 11% in the cys-leukotriene receptor antagonist group, and 15% in the control group.

For patients with aspirin-exacerbated respiratory disease, cys-leukotriene receptor antagonist therapy appears to reduce the rate of lower respiratory tract reactions while increasing the rate of upper airway reactions. This shift in target organ responses is not accompanied by any change in the percentage of false-negative challenges in patients taking LTMDs. Patients taking LTMDs as controller medication should continue to take these drugs when undergoing oral ASA challenges.

COMMENT: *The effect of LTMDs on ASA-induced asthma and rhinitis reactions has been a confusing area since these agents were introduced several years ago. Although it was clear early on that LTMDs failed to prevent these reactions completely in most cases, the Scripps Clinic ASA challenge data base has provided more detailed observations. It appears that the LTMDs attenuate the reactions by selectively reducing the lower airway response, thereby shifting some patients to an isolated upper airway response.*
S. A. T.
Berges-Gimeno MP, Simon RA, Stevenson DD: The effect of leukotriene-modifier drugs on aspirin-induced asthma and rhinitis reactions.
Clin Exp Allergy 32:1491-1496, 2002. ♦♦

PATIENTS with aspirin-exacerbated respiratory disease (AERD) have chronic rhinitis, nasal polyps, and asthma, with attacks of asthma and rhinitis triggered by aspirin or other nonsteroidal anti-inflammatory drugs. Oral aspirin challenges suggest a 9% to 20% prevalence of AERD among adult patients with asthma, even higher in asthma patients with nasal polyps and sinusitis. The clinical findings and natural history of a large group of patients with AERD were analyzed.

The reports included 300 patients with AERD referred to a clinical research center for aspirin desensitization. The patients were 171 women and 129 men, mean age at onset 33 and 35 years, respectively. In all cases, the presence of AERD was confirmed by 3-day, single-blind oral aspirin challenge. Two-thirds of patients had a history of positive wheal and flare skin test results from previous allergy testing, plus positive skin test results to one or more common allergens. One-third of patients had two previous reactions to nonsteroidal anti-inflammatory drugs, including aspirin, while 36% had had more than three reactions. Aspirin was the most common triggering agent, followed by ibuprofen. All patients were taking some kind of treatment before referral, mainly nasal, inhaled, and systemic corticosteroids. Of patients referred in 1998 or after, 60% of patients were taking leukotriene modifiers.

The findings in this large referral series suggest that AERD affects both sexes, usually beginning in the third decade of life. Patients experience steady disease progression, including recurrent sinusitis, nasal polyps, loss of smell, and asthma. In most cases, the disease is severe enough to require controller medications. There is no evidence that AERD has any ethnic or familial predisposition.

COMMENT: *These authors have continued to add to our understanding of AERD, which appears to be a progressive disease of adulthood that can co-exist with other atopic diseases. Now if they could only come up with a safe and easy aspirin desensitization protocol we'd all be happy!*
A. M.
Berges-Gimeno MP, Simon RA, Stevenson DD: The natural history and clinical characteristics of aspirin-exacerbated respiratory disease.
Ann Allergy Asthma Immunol 89:474-478, 2002. ♦♦

IV Vitamin K_1 Has Low Incidence of Anaphylaxis

PREVIOUS reports have described anaphylactic reactions to IV phytonadione, or vitamin K_1. The true incidence of this complication is unknown; it is attributed to the solubilizing vehicle polyethoxylated castor oil, rather than to phytonadione itself. A 58-month, single center review was performed to assess the incidence of anaphylaxis after IV phytonadione administration.

The study was conducted at a large academic medical center with an average of about 900 occupied beds/d. Throughout the period studied, the hospital had a specific protocol for IV administration of phytonadione. A total of 6,572 doses of IV phytonadione in 2,938 patients were included in the analysis. Anaphylaxis occurred at a rate of 3 cases per 10,000 doses of IV phytonadione, 95% confidence interval 0.04 to 11 per 10,000 doses. Two cases are reported in detail.

The analysis suggests a low incidence of anaphylaxis after IV phytonadione administration, similar to that of other drugs associated with anaphylaxis. The findings question the need for antihistamine or corticosteroid pretreatment in patients receiving this vitamin K_1 preparation.

COMMENT: *These observations are important for all allergy specialists. Although the risk appears low, increased awareness should result in timely treatment and avoidance of unnecessary pretreatment.*
A. M.
Riegert-Johnson DL, Volcheck GW: The incidence of anaphylaxis following intravenous phytonadione (vitamin K_1): a 5-year retrospective review.
Ann Allergy Asthma Immunol 89:400-406, 2002. ♦♦

More on the Hygiene Hypothesis

ENDOTOXIN is a proinflammatory agent that is present in house dust and associated with measures of asthma severity. Endotoxin induces Th1 cytokines in human peripheral blood cells, leading to the suggestion that being exposed to endotoxin at some critical time of life might shift the immune system to a predominant Th1-type response. In a previous study, the authors found that exposure to house dust endotoxin (HDE) increased the rate of wheezing in infants with a ➤➤

familial predisposition to asthma and allergies. Older siblings of these infants were studied to examine the longitudinal effects of HDE and other exposures on the risk of wheezing.

The analysis included 226 children aged 5 years or younger, who were siblings of the index children enrolled in the Epidemiology of Home Allergens and Asthma study. At baseline, house dust samples were obtained for measurement of endotoxin and allergen levels. The children were followed up for 4 years to assess the effects of HDE, allergen levels, and pet exposure on wheezing risk over time.

Children exposed to HDE levels higher than the median were at increased risk of wheezing throughout follow-up, multivariate relative risk 1.52 (95% confidence interval 1.07 to 2.14). However, this risk decreased sharply with follow-up. Wheezing risk was also increased for children exposed to higher levels of cockroach allergen. However, wheezing risk was decreased for children exposed to cat allergen and for those with a dog at home. The percentage of children with wheezing decreased during follow-up, from 25.2% at baseline to 12.7% at 4 years.

In young children with a family history or allergy or asthma, exposure to high levels of HDE is associated with an increased risk of wheezing. However, wheezing risk decreases rapidly over time, indicating a possible protective effect of HDE exposure against further episodes of wheezing as children age. Regardless of the influence of HDE, exposure to pets is associated with a reduced risk of wheezing. These results suggest that the effects of HDE and pet exposure on the developing immune system may occur through separate mechanisms.

COMMENT: *Just when we thought we could explain the hygiene hypothesis by exposure to endotoxin, along comes this study from Harvard. Using siblings from their ongoing cohort sample, these researchers followed children for 4 years, monitoring exposure to HDE and pets. Although the study was only looking for wheezing and did not accurately define asthma, the children with high HDE exposure had a higher rate of wheezing initially. The wheezing rate decreased over time. It was also surprising that the associated risk ratios of wheeze with HDE and animal exposure did not change significantly from their separate univariate models. Therefore there may be different mechanisms that mediate the effects of HDE and pet exposure on the developing immune system.*
S. M. F.

Litonjua AA, Milton DK, Celedon JC, and others: A longitudinal analysis of wheezing in young children: the independent effects of early life exposure to house dust endotoxin, allergens, and pets.
J Allergy Clin Immunol 110:736-742, 2002. ♦♦

STUDIES evaluating the so-called hygiene hypothesis have suggested that exposure to bacterial endotoxin during early childhood may protect against the development of allergy. However, there are few data on how exposure to house dust endotoxin affects cellular immune reactivity in children. The effects of exposure to endotoxin and to mite and cat allergen on expression of chemokine receptors mediating cell migration were studied in a population-based sample of infants.

One hundred thirty-five children from an ongoing birth cohort study were studied at 2 years of age. The children were 76 boys and 59 girls. Sixty percent had a parental history of atopy and 52% were breast-fed exclusively for at least 6 months. Blood samples were obtained for measurement of peripheral blood CD4+ and CD8+ T-cell subsets; the chemokine receptors CCR5 and CCR3 were analyzed as markers of type 1 and 2 T cells. When the children were 3 months old, samples of dust from their mothers' mattresses were obtained for measurement of endotoxin and mite and cat allergen.

Endotoxin levels in the mothers' mattresses varied widely, with a median concentration of 1,948 EU/m². House dust mite allergen level also varied, with a median value of 675 ng/m². Median proportion of CCR5+ T cells was 3.4% in CD8+ cells and 5.4% in CD4+ cells. Proportions of CCR3+ T cells were significantly lower: 0.03% and 0.06%, respectively.

There was a positive association between endotoxin level and the proportion of type 1 CCR5+ cells in the CD4+ T cell subset. In contrast, levels of cat allergen were associated with high proportions of type 2 CCR3+ cells. In the CD8+ T cell subset, mite allergen level was inversely related to the proportion of CCR5+ or CCR3+ cells, while cat allergen level was positively associated with proportions of both CCR5+ and CCR3+ cells.

Early exposure to endotoxin may favor the development of type 1 CD4+ T cells in young children, this prospective study suggests. In contrast, exposure to mite or cat allergen may influence the proportion of both type 1 and type 2 CD8+ cells. The protective effects of high exposure to cat allergen associated with increased proportions of CCR5+ CD8+ T cells might be more marked in children without a parental history of atopy.

COMMENT: *This report from Germany is of interest particularly because of its prospective design. Measuring chemokine receptors CCR5 (Th1) and CCR3 (Th2) for both CD4+ and CD8+ cells in 135 children aged 2 years, the researchers compared these cellular responses with the amount of endotoxin, mite, and cat dander allergen content in their mothers' mattresses at 3 months of age. (The children slept on their mothers' mattresses during their first months of life.) The findings support the hygiene hypothesis and previous reports that endotoxin exposure tends to promote type 1 CD4+ T cells. In contrast, mite was associated with a decrease in CCR5+ (Th1) CD8+ T cells. This suggests that there may be a protective effect of high cat allergen levels causing the increased Th1 response. In either case, this study adds fuel to the fire in the proof of the hygiene hypothesis.*
S. M. F.

Bolte G, Krass-Etschmann S, Konstantopoulos N, et al, for the LISA Study Group: Different effects of endotoxin versus mite and cat allergen exposure on T-cell differentiation in infants.
J Allergy Clin Immunol 2002; 110:634-640. ♦♦

Regular Inhaled Steroid Use Lowers Risk of Asthma Hospitalization

FOR patients with asthma, inhaled corticosteroids reduce morbidity and mortality. However, most studies of this treatment have evaluated only short-term effects. The effects of inhaled corticosteroid use on long-term rates of hospitalization for asthma were evaluated.

A Canadian provincial health data base was used to identify two population-based cohorts of asthma patients aged 5 to 44 years. The full cohort included all patients beginning at the start of asthma treatment, while the hospitalized cohort including patients hospitalized for asthma beginning at the date of hospital discharge. Patients were followed up to hospitalization or rehospitalization for asthma, respectively. Cases were matched for calendar time and markers of asthma severity to controls within the cohort.

Of 30,569 patients in the full cohort, 3,894 were hospitalized and 1,886 were rehospitalized during follow-up. The annual rate of asthma hospitalization was 42.4/1,000 asthma patients. The risk of asthma hospitalization was 31% lower for patients who regularly used inhaled corticosteroids, while the risk of rehospitalization was 39% lower. The protective effect of regular inhaled corticosteroid use was well maintained over follow-up.

This large, population-based study supports the effectiveness of regular inhaled corticosteroid use in preventing hospitalization for asthma. The benefits are greatest in patients at highest risk: those with a previous history of asthma hospitalization. The benefits of inhaled corticosteroids for patients with asthma depend on regular use.

COMMENT: *This well-regarded Canadian group employed the Saskatchewan Health data bases to constitute two large cohorts of asthma patients. One group was studied from the inception of treatment, the other following discharge from the hospital. The study found that, over the long-term, regular use of inhaled corticosteroids reduced the rate of hospital admissions by one-third. Interestingly, the reduction was more pronounced in the more severe cohort, ie, those with prior admission. The authors strongly point out that it was not the use--but the regular use--of inhaled corticosteroids that was essential to the efficacy of treatment.*
E. J. B.

Suissa S, Ernst P, Kezouh A: Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma.
Thorax 57:880-884, 2002. ♦♦

Antimicrobial Peptides Are Reduced in Atopic Dermatitis Skin

THE innate defense system of the skin includes the cathelicidins (LL-37) and β-defensins, peptides with antimicrobial activity against bacteria, fungi, and viruses. These peptides may accumulate in skin affected by psoriasis and other inflammatory diseases. Recurrent infection of skin lesions is a common problem in patients with atopic dermatitis (AD). Levels of two endogenous antimicrobial peptides--LL-37 and human β-defensin-2 (HBD-2)--were compared in skin from patients with AD, psoriasis, and healthy controls.

Skin punch biopsy specimens were obtained from 8 patients with moderate to severe AD, 11 patients with psoriasis, and 6 healthy controls. Immunohistochemical staining was performed to measure expression of the LL-37 and HBD-2 proteins. In further studies, reverse-transcriptase-polymerase chain reaction (RT-PCR) was performed to confirm relative expression of mRNA for both peptides and a colony-forming assay was used to test their antimicrobial activity against *Staphylococcus aureus*.

The immunohistochemical studies confirmed high expression of both LL-37 and HBD-2 in the skin of patients with psoriasis. In contrast, patients with AD showed low expression of both peptides in acute as well as chronic skin lesions. In the RT-PCR assays, expression of mRNA for LL-37 and HBD-2 was substantially lower in AD lesions than in psoriasis lesions. The two peptides had synergistic activity against *S. aureus* in the concentrations found in psoriatic skin, but not in AD skin.

In patients with AD, susceptibility to skin infection by *S. aureus* may be related to a failure of the skin's innate immune defense system. Skin lesions from AD patients are deficient in two antimicrobial peptides, LL-37 and HBD-2. This finding might be explained by high levels of the type 2 helper cytokines interleukin-4 and interleukin-13 in AD skin.

COMMENT: *Patients with atopic AD are highly susceptible to bacterial and viral infections compared to normals and people with other disruptive skin diseases like psoriasis. This study showed that two naturally occurring skin peptides--HBD-2 and LL-37, components of the innate immune system in skin--are deficient in AD skin compared with psoriatic or normal skin. The low levels of these two peptides from AD skin were unable to kill* S. aureus. *This may help explain the increased prevalence of skin infection in AD.*
R. J. M.

Ong PY, Ohatke T, Brandt C, et al: Endogenous antimicrobial peptides and skin infections in atopic dermatitis.
N Engl J Med 347:1151-1160, 2002. ♦♦

Skin Prick Testing Predicts Absence of Asthma in Young Patients

IN patients with typical asthma symptoms and normal spirometry results, definitive diagnosis of asthma requires bronchial hyperresponsiveness to nonspecific stimuli. Skin prick testing (SPT) is a simple and quick means of assessing atopy; positive SPT results are correlated with the presence of asthma and the degree of bronchial hyperresponsiveness. However, there are few data on the significance of a negative SPT result in a patient with clinical evidence of asthma. The role of SPT in the diagnostic workup of suspected asthma was evaluated in young adults with suspected asthma.

Three groups of subjects were identified in an Israeli military outpatient clinic: 175 patients with active ➤➤

asthma; 100 controls with no asthma or allergic rhinitis; and 150 patients with suspected asthma, presenting with dyspnea and/or chronic cough. All patients in the suspected asthma group had normal results on spirometry results and exercise challenge testing. All three groups underwent SPT using a battery of common allergens; the patients with suspected asthma underwent methacholine challenge testing as well.

The rate of positive SPT results to one or more aeroallergens was 95% in the patients with active asthma, 54% in the control group, and 69% in the patients with suspected asthma. In all three groups, house dust mite was the most frequent sensitivity. The SPT results were significantly correlated with those of methacholine challenge testing, which showed bronchial hyperreactivity in 50% of the patients with suspected asthma: 65% of patients with a positive SPT vs 15% of those in whom SPT was negative. Skin prick testing had a diagnostic sensitivity of 91%, with specificity of 52% and negative predictive value of 85%.

In young adults with suspected asthma, a negative result on SPT is strongly correlated with the absence of bronchial hyperreactivity on methacholine challenge testing. Skin prick testing may provide a simple, quick, and inexpensive test to predict the absence of asthma in this group of patients. Only those patients with a positive result on SPT should proceed to exercise or methacholine challenge testing.

COMMENT: *Have you ever wondered about the positive and negative predictive value of allergy skin tests in helping to establish the diagnosis of asthma? Graif and colleagues do just this in young adults with suspected asthma and normal pulmonary function tests. These investigators find that negative allergy skin tests correlate extremely well with negative methacholine challenge. Thus in many young adults, methacholine testing may be unnecessary if allergy skin tests are negative. This is an extremely cost-effective approach and seems quite sensible to this allergist.*
A. L. L.

Graif Y, Yigla M, Tov N, Kramer MR: Value of a negative aeroallergen skin-prick test result in the diagnosis of asthma in young adults: correlative study with methacholine challenge testing.
Chest 122:821-825, 2002. ♦♦

UNIFIED AIRWAY DISEASE: PRO AND CON

Study Looks at Links Between Allergic Rhinitis and Asthma

SOME reviews have suggested that allergic rhinitis and asthma are closely related conditions, and even that they represent differing manifestations of a single disease entity. Data from a prospective, population-based study were used to analyze the relationship between allergic rhinitis and allergic asthma.

The study included 734 Copenhagen residents, aged 15 to 69 years in 1990 when they responded to an initial screening questionnaire. All were examined on two occasions during an 8-year follow-up period. Allergic rhinitis and asthma to pollen were defined on the basis of relevant symptoms after exposure to grass, trees, or flowers and by the presence of IgE antibodies to birch, grass, or mugwort. Symptoms and antibodies in response to animals or dust mite were examined as well.

Fifty-two subjects had allergic asthma to pollen. At follow-up, all 52 subjects had allergic rhinitis to pollen as well. Eighty-nine percent of subjects with allergic asthma to animals also had allergic rhinitis to animals; 95% of subjects with allergic asthma to mite had allergic rhinitis to mite. Overall, just 1 subject with allergic asthma at follow-up did not have allergic rhinitis at baseline or follow-up.

Twenty-eight incident cases of allergic asthma developed during follow-up. Eighteen of these subjects had allergic rhinitis to pollen at baseline and 10 had allergic rhinitis to pollen at follow-up.

Nearly all subjects with allergic asthma have allergic rhinitis as well. The link between rhinitis and asthma appears stronger for subjects with animal or mite allergy than for those with pollen allergy. These findings add to the evidence that allergic rhinitis and asthma represent a continuum of disease, rather than distinct entities.

COMMENT: *This study focused on the relationship between allergic rhinitis and allergic asthma. More than 700 subjects were examined in 1990 and again in 1998. At follow-up, all subjects with allergic asthma to pollen had developed new-onset allergic rhinitis. The results support the hypothesis that allergic rhinitis and allergic asthma are manifestations of the same disease entity.*
E. J. B.

Linneberg A, Nielsen NH, Frφlund L, et al: The link between allergic rhinitis and allergic asthma: a prospective population-based study. The Copenhagen Allergy Study.
Allergy 57:1048-1052, 2002. ♦♦

Worsening Rhinitis Predicts Worsening Asthma During Pregnancy

ABOUT one-third of women with asthma will have worsening of their disease during pregnancy. However, the mechanisms and predictors of worsening remain uncertain. Potential predictors of the course of asthma during pregnancy were analyzed.

The analysis included 568 women enrolled in a previous prospective study of asthma during pregnancy. In response to a questionnaire, 34% of the women said their asthma had improved during pregnancy, 36% that it had gotten worse, and 26% that it was unchanged. Maternal or pregnancy-related predictors of asthma course during pregnancy were analyzed.

Of the patient-related factors assessed, the only significant variable was the course of rhinitis during pregnancy. Fifty-one percent of women whose asthma improved during pregnancy also reported an improvement in rhinitis; conversely, 56% of those whose ➤➤

rhinitis got worse also had worsening of asthma during pregnancy. Asthma was somewhat more likely to worsen in multiparas and in women who delivered during the winter, but these relationships were nonsignificant. The course of asthma during pregnancy was unrelated to the mothers' demographic characteristics, panic-fear scale, smoking, maternal weight, pre-eclampsia or preterm birth, or infant weight and sex.

The course of rhinitis during pregnancy is the only significant predictor of the course of asthma during pregnancy. The mechanisms of this relationship, and the possible benefits of treating worsening rhinitis during pregnancy, require further study. Many other factors previously reported or suspected to influence the course of asthma during pregnancy were not significant in this study.

COMMENT: *The management of asthma in a pregnant woman is a common clinical problem. Reluctance to use pharmacologic therapies complicates management, making any findings that predict worsening of asthma very useful. Factors historically or intuitively suspected to affect asthma in pregnancy were not found to affect outcomes in this paper. These included weight gain, gender of fetus, cigarette smoking, season of delivery, panic, or anxiety. The severity of rhinitis correlated with severity of asthma. Thus, again we learn the importance of evaluating the entire airway.*
D. K. L.
Kircher S, Schatz M, Long L: Variables affecting asthma course during pregnancy.
Ann Allergy Asthma Immunol 89:463-466, 2002. ♦♦

Very-Low-Dose Allergen Challenges Cause Airway Inflammation in Nonasthmatic Rhinitis Patients

BY the time asthma is diagnosed, permanent airway "remodeling" is already present. Allergen challenges can be used to study asthma pathophysiology; repeated allergen challenges over a few days may lead to increasing allergen-induced airway responses. A very-low-dose allergen challenge protocol was used to assess lower airway inflammation among subjects with nonasthmatic allergic rhinitis (NAAR), compared to patients with mild allergic asthma.

The study included 14 subjects with NAAR and 11 with allergic asthma, all studied out of pollen season. Baseline tests included skin prick testing to common aeroallergens, spirometry, methacholine challenge, and blood and induced sputum differential cell counts. On 4 consecutive days, the subjects were challenged with a very low dose of allergen. All tests were repeated 6 hours after the second and fourth allergen challenges and again after 1 week. Lower airway inflammatory changes were compared for the NAAR and asthmatic groups.

The very-low-dose allergen challenges produced no significant changes in FEV_1 or PC_{20} in either group. However, after the second allergen challenge the NAAR subjects showed a significant increase in the mean percentage of eosinophils in induced sputum. Sputum eosinophils decreased in most subjects after the fourth allergen challenge, and generally returned to normal by the 1-week follow-up point. In the patients with mild allergic asthma, sputum eosinophils were nonsignificantly increased after the second challenge. After the fourth challenge, eosinophils were decreased in 4 of the 11 asthma patients.

Sputum and blood eosinophil counts did not vary significantly for subjects were positive vs negative for house dust mite. At all times, the asthma patients had higher mean eosinophil cationic protein levels than the NAAR subjects. This variable increased nonsignificantly after the second challenge in the NAAR group. Blood inflammatory cell levels did not increase after allergen challenge.

In subjects with NAAR, as in those with allergic asthma, repeated challenges with very low doses of allergen lead to increased airway eosinophilia. This change occurs despite the absence of increased airway responsiveness, airflow obstruction, or asthmatic symptoms. Thus lower airway inflammation may precede clinical symptoms or airway hyperresponsiveness. It remains unclear why some patients with allergic rhinitis go on to develop asthma while others do not.

COMMENT: *Previous studies have shown that inhaled allergen provocation in allergic rhinitis subjects without asthma results in an increase in sputum eosinophilia without changing bronchial responsiveness to methacholine. This study used a very low dose of inhaled allergen daily for 4 days to compare the response of allergic asthmatics and allergic nonasthmatics. While the allergen challenge resulted in increased sputum eosinophilia in both asthmatics and nonasthmatics, the nonasthmatics experienced a much more rapid resolution of their sputum eosinophilia. Furthermore, in 12 of the 13 nonasthmatic subjects, a significant improvement in sputum eosinophilia happened before the last of the daily allergen challenges had occurred. Although preliminary, this provocative (excuse the pun) result suggests that the lower airway response of nonasthmatic subjects with allergic rhinitis has the capacity to recover in the midst of an allergic insult.*
S. A. T.
Boulay M-E, Boulet L-P: Lower airway inflammatory responses to repeated very-low-dose allergen challenge in allergic rhinitis and asthma.
Clin Exp Allergy 32:1441-1447, 2002. ♦♦

Early Exposure to Children Lowers Hay Fever Risk, But Increases Asthma Risk s

PART of the "hygiene hypothesis," is that close contact with other children early in life presents a microbial challenge, promoting nonallergic development of the immune system. This effect might be expected to be mediated through IgE production, as the ➤➤

exposure to other children at home and in day care on the development of asthma and hay fever in adulthood were assessed, including the effects on specific IgE production.

The analysis was based on the European Community Respiratory Health Survey, which included more than 18,500 adults, aged 20 to 44 years, from 36 areas across Europe. All subjects provided information childhood exposure variables and adult asthma and hay fever. In addition, specific IgE measurements were available in nearly 14,000 subjects.

Having many siblings was associated with a reduced risk of hay fever in adulthood, odds ratio (OR) 0.92. In contrast, there was a U-shaped relationship between number of siblings and adult asthma. The rate of hay fever was also reduced for subjects who had no symptoms but were exposed to other children in day care, OR 0.76. However, the same group of subjects was at higher risk of asthma, OR 1.48 for wheezing. The relationships between childhood exposures and adult respiratory symptoms were unaffected by adjustment for specific IgE measurements.

Early exposure to other children, at home or in day care, is associated with a lower rate of hay fever but a higher rate of asthma in young adulthood. The findings are strengthened by their consistency across the diverse settings studied. These effects are not mediated by changes in atopic sensitization. The findings are discussed in light of their implications for the hygiene hypothesis: the antimicrobial challenge of exposure to other children may promote nonallergic immune system development, while a higher rate of clinical infections may adversely affect the lungs.

COMMENT: *This very large European study investigated the impact of exposure to children within the family and in day care centers on subsequent development of allergic rhinitis and asthma. The strength of this study was its ability to compare findings between 36 socioculturally, genetically, and geographically different areas of Western Europe. Exposure to many children at home or in day care was associated with less allergic rhinitis but more asthma in adult life. This study adds to the ample evidence showing decreased allergic rhinitis with exposure to children at a young age. It also adds to the inconclusive evidence that exists between exposure to children of a young age and subsequent development of asthma.*
E. J. B.

Svanes D, Jarvis D, Chinn S, et al, for the European Community Respiratory Health Survey: Early exposure to children in family and day care as related to adult asthma and hay fever: results from the European Community Respiratory Health Survey.
Thorax 57:945-950, 2002. ♦♦

Exhaled Leukotriene Levels Are Related to Asthma Severity in Children

THE various cysteinyl leukotrienes (cys-LTs) are linked to airway smooth muscle contraction, increased vascular permeability, and mucous hypersecretion. In contrast, leukotriene B_4 (LTB_4) is a potent neutrophil chemoattractant and activator. These two leukotrienes were measured in exhaled breath condensates of children with asthma, including analysis of the effects of steroid treatment.

Four groups of 7- to 14-year-old children were studied: 11 healthy, nonatopic controls; 11 patients with mild, intermittent asthma who had not been treated with steroids; 13 with mild, persistent asthma receiving low-dose inhaled steroids; and 13 with moderate to severe persistent asthma receiving high-dose inhaled steroids. Exhaled breath condensates were obtained for measurement of cys-LTs and LTB_4 using a specific enzyme immunoassay.

Exhaled LTB_4 levels were 47.9 pg/mL in controls and 52.7 pg/mL in children with mild intermittent asthma, compared with 126.0 pg/mL in children with mild persistent asthma and 131.9 pg/mL in those with moderate to severe persistent asthma. Levels of cys-LTs were 18.5, 19.9, 27.9, and 31.5 pg/mL, respectively. The children with mild persistent asthma showed a significant, inverse correlation between cys-LTs and LTB_4 in exhaled breath condensates.

Cysteinyl leukotrienes and LTB_4 are detectable in exhaled breath condensates in healthy children and children with asthma. Both exhaled leukotriene levels are significantly increased in children with persistent asthma, compared to normals and children with mild intermittent asthma. They may provide useful noninvasive indicators of airway inflammation in children with asthma.

COMMENT: *The search for a noninvasive measure of airway inflammation in asthma continues. This report suggests that exhaled LTB_4 and cys-LTs are increased with severity of asthma, compared with normal, nonasthmatic controls. Interestingly, both LTB_4 (a potent neutrophil chemotaxin) and the proinflammatory cys-LT were increased with disease severity. These data imply that development of a simple, office-based measure of exhaled LTs might be a useful tool in assessing airway reactivity as well as response to anti-inflammatory therapy, at least in childhood asthma.*
G. D. M.

Csoma Z, Kharitonov SA, Balint B, et al: Increased leukotrienes in exhaled breath condensate in childhood asthma.
Am J Respir Crit Care Med 166:1345-1349, 2002. ♦♦

Lactic Acid Bacteria Inhibit Type 2 Cytokine Production

EVIDENCE suggests that changes in the intestinal bacterial flora or lack of bacterial stimulation during childhood may predispose to the development of allergic diseases. Studies of dietary lactic acid bacteria (LAB), used in fermented food products, have shown potential health benefits in humans, including reduced allergy symptoms. The effects of dietary LAB on production of type 2 cytokines were studied in vitro.

The investigators prepared peripheral blood mononuclear cell cultures from asthmatic patients allergic to house dust mite and from healthy donors. Both ➤➤

cultures underwent 48 hours of stimulation with *Dermatophagoides pteronyssinus* allergen or a staphylococcal superantigen previously shown to produce high levels of Th2 cytokines. The effects of preincubation with four different LAB strains on production of type 2 cytokines were studied using specific enzyme-linked immunosorbent assays.

Preincubation with live strains of LAB significantly inhibited the secretion of Th2 cytokines: interleukin-4 and interleukin-5. The effect was similar for all LAB strains tested and occurred in dose-dependent fashion. In further experiments, the mechanism of cytokine inhibition by LAB appeared to involve production of interleukin-12 and interferon- γ .

In this in vitro study, preincubation with LAB strains inhibits the production of Th2 cytokines. The findings suggest that treatment with LAB might help to restore the host's ability to mount a limited response to aeroallergens, thus preventing allergic disease.

COMMENT: *Intriguing data are emerging to suggest that ingestion of common nonpathogenic bacteria may have an antiallergic effect. In this in vitro study, peripheral blood mononuclear cells from allergic people were preincubated with LAB before stimulation with relevant allergen, and resultant Th2 cytokines were measured. A dose-related inhibition of cytokine production was observed in LAB systems, but not in control* Escherichia coli *systems. More research on feeding of so-called probiotics to babies at risk for atopy is needed.*
R. J. M.

Pochard P, Gosset P, Grangette C, et al: Lactic acid bacteria inhibit T_{H2} cytokine production by mononuclear cells from allergic patients.
J Allergy Clin Immunol 110:617-623, 2002. ♦♦

No Association Between Serum ECP and Methacholine BHR in Infants with Recurrent Wheezing

THERE is ongoing debate over the diagnostic and management techniques used in childhood asthma. Studies attempting to correlate serum eosinophil cationic protein (ECP) with asthma symptoms or bronchial hyperreactivity (BHR) have yielded conflicting results. To evaluate eosinophilic inflammation as a predictor of asthma risk, the correlation between serum ECP and BHR was assessed in a group of infants with recurrent wheezing.

The study included 72 infants, median age 15 months, with a history of recurrent wheezing. All underwent measurement of serum ECP and BHR to methacholine. Serum ECP levels were classified as low, mean 6.6 μg/L, in 22 patients; medium, 14.3 μg/L, in 23 patients; and high, 34.5 μg/L, in 27 patients. Mean provocative methacholine concentrations were 350.9 μg/L in the low ECP group, 340.7 μg/L in the medium ECP group, and and 301.3 μg/L in the high ECP group. Across groups, serum ECP levels were not significantly correlated with bronchial reactivity.

Infants with recurrent wheezing show no correlation among serum ECP, methacholine responsiveness, and atopy. Serum ECP and BHR thus seem to represent independent pathogenic mechanisms of childhood asthma.

COMMENT: *These findings represent another important step in our understanding of the pathogenesis of asthma. While serum ECP has been touted as a potential measure of asthma severity, its lack of correlation with methacholine responsivity clearly limits its usefulness. Clearly there is no* single *laboratory* or *clinical standard to measure asthma severity. Thank God we still need good doctors!*
A. M.

Reichenbach J, Jarisch A, Khan S, et al: Serum ECP levels and methacholine challenge in infants with recurrent wheezing.
Ann Allergy Asthma Immunol 89:498-502, 2002. ♦♦

Fexofenadine vs Desloratadine for Allergic Rhinitis: Placebo-Controlled Trial

FOR patients with allergic rhinitis, both fexofenadine and desloratadine are clinically safe and effective when given once daily. In in vitro studies, desloratadine shows substantially greater H_1-receptor antagonist potency than fexofenadine; however, the clinical relevance of this difference is unknown. The relative efficacy of these two antihistamines was assessed in patients with allergic rhinitis.

Forty-nine patients with seasonal allergic rhinitis were studied during grass pollen season. In randomized, crossover fashion, they received 2 weeks of treatment with fexofenadine, 180 mg/d; and desloratadine, 5 mg/d. Between treatments, the patients received 7 to 10 days of placebo. Daily measurements of peak nasal inspiratory flow and nasal symptoms were obtained.

Compared with placebo, both fexofenadine and desloratadine were superior in increasing peak nasal inspiratory flow and reducing nasal symptoms, including nasal blockage and irritation. Nasal discharge and eye symptoms did not differ significantly during between active treatment and placebo. On comparison of relative efficacy, fexofenadine and desloratadine performed similarly well in improving nasal inspiratory flow and nasal symptoms. On a 12-point scale, scores for total nasal symptoms were 3.2 for fexofenadine and 3.4 for desloratadine.

Once-daily fexofenadine and desloratadine offer similar clinical performance in patients with seasonal allergic rhinitis. On both objective and subjective measures, the two medications are comparable to each other and superior to placebo. The in vitro differences in potency do not translate into a clinically significant difference in efficacy.

COMMENT: *While antihistamines in general are not potent decongestants, there have been data published suggesting their efficacy relative to placebo. This head-to-head, placebo-controlled, crossover comparison suggests that both desloratadine and fexofenadine have statistically significant effects on nasal congestion, although in this study the congestion was fairly* ➤➤

although in this study the congestion was fairly mild. Interestingly, neither drug resulted in a significant improvement in ocular symptoms.
S. A. T.
Wilson AM, Haggart K, Sims EJ, Lipworth BJ: Effects of fexofenadine and desloratadine on subjective and objective measures of nasal congestion in seasonal allergic rhinitis. ♦♦
Clin Exp Allergy 32:1504-1509, 2002.

Anti-IgE Affects Leukotriene Pathway in Allergic Children Receiving SIT

SYMPTOMS of IgE-mediated allergy depend on the release of inflammatory mediators such as sulfidoleukotrienes (SLTs) in response to binding to IgE receptors on mast cells and basophils. Omalizumab is a newly developed humanized monoclonal anti-IgE antibody. This in vitro study examined the effects of anti-IgE plus specific immunotherapy (SIT) on the leukotriene pathway in allergic children.

The study included 92 children with seasonal allergic rhinitis who were sensitized to birch and grass pollens. As part of a phase III clinical trial, the patients were randomized to receive birch or grass SIT for at least 14 weeks before the start of the birch pollen season. After a 12-week SIT titration period, they were further randomized to receive 24 weeks of treatment with anti-IgE or placebo. In vitro allergen stimulation studies were performed to examine the effects of SIT plus anti-IgE therapy on release of SLTs by blood cells.

The clinical trial showed significant reductions in rhinitis symptoms during pollen season in children receiving anti-IgE in addition to SIT. At the end of treatment, in vitro studies demonstrated much lower release of SLTs in patients receiving anti-IgE plus either form of SIT. This was so compared with pretreatment values or with the placebo groups, which showed no change in SLT release in response to allergen. Patients in the anti-IgE groups also had significantly lower SLT release in response to stimulation with allergens not included in their SIT regimens.

In children with allergic rhinitis, adding anti-IgE therapy to SIT significantly influences the leukotriene pathway, regardless of the type of SIT allergen used. This change is at least weakly correlated with the reduction in symptom load noted in patients receiving anti-IgE plus SIT.

COMMENT: *As we await FDA approval, there has been much discussion about the potential roles for anti-IgE therapy. These European investigators added anti-IgE to the regimen of aqueous SIT in children with grass or tree pollen rhinitis. A strength of their findings is that both symptoms and leukotriene release were significantly improved in the group that received anti-IgE. A weakness is the short duration of therapy, since the children were only receiving their SIT for 12 weeks when they were randomized and the data were analyzed after only 24 weeks. Although the doses of SIT seemed reasonable, there was no information related to shot reactions or whether these were improved in the group receiving anti-IgE. This report clearly shows that there are both immunologic and clinical benefits to the combination of SIT and anti-IgE. The question of how long these effects are maintained remains unanswered, for now.*
S. M. F.
Kopp MV, Brauberger J, Riedinger F, et al: The effect of anti-IgE treatment on in vitro leukotriene release in children with seasonal allergic rhinitis. ♦♦
J Allergy Clin Immunol 110:728-735, 2002.

Avoidance Measures Reduce Rate of Mite Sensitization in Children

SENSITIZATION to mite allergen has a major impact on the development of asthma and related morbidity in children. The effects of a simple allergen avoidance intervention on the rate of mite sensitization in young children were evaluated in a multicenter, randomized, single-blind trial.

The study included 636 toddlers and preschool children, mean age 3 years, from four European countries. All children were considered at risk for allergies because they had one or more parents with atopic symptoms and sensitization; children with initial sensitization to mite were excluded. One group of children were assigned to a simple avoidance intervention, consisting of a special mite-impermeable mattress cover and advice on mite reduction. Recommended measures included removing carpets from the child's room, weekly washing of soft toys and bedding, frequent vacuuming when the child was not present, and keeping pets out of the child's room. Mite sensitization was assessed by skin prick or specific IgE testing.

One-year follow-up data were available on 566 children. On intention-to-treat analysis, the rate of mite sensitization was 3% in the intervention group vs 6.5% in the control group. Children who became sensitized to mite were more likely to have allergic symptoms and to have received a physician diagnosis of asthma, eczema, or food allergy.

In high-risk toddlers and preschoolers, a relatively simple allergen avoidance program can reduce the rate of sensitization to dust mite. More study is needed to determine whether prolonged avoidance has a sustained primary preventive effect on sensitization, as well as a secondary prevention effect in lowering the risk of allergic symptoms.

COMMENT: *We give immunizations to children to prevent the development of infectious diseases--wouldn't it be nice if we could confidently recommend a safe intervention for children to prevent the development of allergies? The European SPACE (Study on Prevention of Allergy in Children in Europe) Group reports a carefully designed prospective study that used mattress covers and additional environmental control advice as the intervention variables to check for their effect on the development of allergies in infants and toddlers. Although the numbers were small and there was some variation among the sites, there was an impressive 50% reduction in the development of allergies in the* ➤➤

from the SPACE group's data as their kids grow.
S. M. F.
Tsitoura S, Nestoridou K, Botis P, et al, for the SPACE Group: Randomized trial to prevent sensitization to mite allergens in toddlers and preschoolers by allergen reduction and education: one-year results.
Arch Pediatr Adolesc Med 156:1021-1027, 2002. ♦♦

REVIEWS OF NOTE

COMMENT: *This excellent review discusses the evidence for adverse health effects of selected air pollutants. Particular attention is focused on airborne particulate matter and ozone. The well-referenced article should prove very useful to the clinician seeking information on this subject.*
E. J. B.
Brunekreef B, Holgate ST: Air pollution and health. **Lancet** 360:1233-1242.

COMMENT: *The prevalence of respiratory allergies seems to be increasing, and the prevalence of* indoor *allergies, especially to mold, is getting ever-more scrutiny. (About 25% of the Earth's biomass is fungi.) Allergists are essential in helping their communities, and the legal system, to understand the complexities of aeroallergen behavior. This short review article summarizes what is known and not known, but it just scratches the surface of the topic.*
R. J. M.
Burge HA: An update on pollen and fungal spore aerobiology. **J Allergy Clin Immunol** 110:544-552, 2002.

COMMENT: *A must-read in this rapidly changing world! Although resumption of universal immunization of the U.S. population is not planned at this time, smallpox immunization has been ordered for military personnel and will be made available to health care and public safety workers in early 2003. It will become available to the general public on a voluntary basis at a later date.*
J. A. A.
American Academy of Pediatrics, Committee on Infectious Diseases: Policy statement: smallpox vaccine. **Pediatrics** 110:841-845, 2002.

COMMENT: *Recognition of rare problems amongst common events in medicine is the daily challenge of the clinician. The challenge is particularly difficult when the drug we use to treat allergy causes allergy. This is a useful compendium of the literature, providing the evidence for allergic reactions to a variety of corticosteroids and offering suggestions for management of corticosteroid-allergic patients.*
D. K. L.
Butani L: Corticosteroid-induced hypersensitivity reactions. **Ann Allergy Asthma Immunol** 89:439-445, 2002.

American College of
Allergy, Asthma & Immunology
85 West Algonquin Road, Suite 550
Arlington Heights, IL 60005-4425