ALLERGYWATCH®

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

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New Reagent Is Sensitive and Specific for Diagnosis of Latex Allergy

A new reagent for diagnosis of latex allergy in high-risk patients--a *Hevea brasiliensis* nonammoniated latex extract--was evaluated for safety and efficacy. The multicenter trial included 324 subjects, 134 with a clinical history of latex allergy. Reagent was prepared from Malaysian *H. brasiliensis* sap. Sequential puncture skin tests were performed at concentrations of 1, 100, and 1,000 μg/mL protein. Glove provocation tests were done to clarify patient status when the history and skin test results did not match.

Fifteen percent of patients with clinical latex allergy had a negative glove provocation test. Forty percent of latex-allergic patients were highly sensitive, with positive skin results at the lowest reagent concentration. Using the new reagent, skin testing had a sensitivity of 95% at the 100 μg/mL concentration and 99% at 1 mg/mL. Specificity values were 100% and 96%, respectively. Mild systemic reactions, none requiring epinephrine treatment, occurred in about 16% of allergic patients and 4% of the control group. The rate of delayed reactions, all of which were mild, was 10% and 3%, respectively. Systemic reactions did not appear any more likely in children than adults.

The new nonammoniated latex extract skin testing reagent appears to be safe and reliable for the diagnosis of IgE-dependent latex allergy. It provides very high diagnostic sensitivity and specificity at concentrations of 100 μg/mL and 1 mg/mL. A clinical history of latex allergy is not sufficient to diagnose latex allergy, as many patients with a positive clinical history will have a negative skin test.

COMMENT: *This study documents the safety along with sensitivity and specificity of a natural rubber latex extract, which it is hoped will be approved for use* ➤➤

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

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

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by the Food and Drug Administration. Fifteen percent of the patients with a history of latex allergy had negative skin tests and provocation tests, suggesting history alone is not accurate in diagnosing latex allergy.
M. S. B.
Hamilton RG, Adkinson NF, and the Multicenter Latex Skin Testing Study Task Force: Diagnosis of natural rubber latex allergy: multicenter latex skin testing efficacy study. **J Allergy Clin Immunol** 102:482-490, 1998. ♦♦

Patients With Self-Reported Asthma Have Faster Declines in FEV_1

THE link between asthma and changes in FEV_1 over time was analyzed using 15-year follow-up data of subjects in the Copenhagen City Heart Study. The analysis included data on more than 17,500 adults; the presence or absence of asthma was determined by the subject's response to the question, "Do you have asthma?" Previous reports from this prospective epidemiologic study had shown a 1.6-fold increase in mortality among patients with self-reported asthma.

The prevalence of self-reported asthma increased from 2.3% at baseline to 3.3% at the second examination to 6.3% at the third examination. The average rate of decline in FEV_1 among subjects completing three examinations was 38 mL per year for those with self-reported asthma versus 22 mL per year for those without asthma. Subjects with mucus hypersecretion and smokers had significantly greater declines in FEV_1, whether or not they had asthma.

The study finds a significant acceleration of the age-related decline in FEV_1 among patients with self-reported asthma. Smoking and mucus hypersecretion are also significant markers of respiratory decline. The findings support the view of asthma as a chronic inflammatory disease that causes irreversible airway fibrosis. Other studies suggest that early inhaled steroid therapy for patients with mild asthma is beneficial, though it remains to be seen whether such treatment can prevent asthma-related declines in lung function.

COMMENT: *This 15-year longitudinal study of Danish citizens found that people with self-reported asthma had a significantly greater decline in FEV_1 over time than people without asthma (38 mL per year versus 22 mL per year). The gap widens with advancing age. The decline was accelerated by chronic mucus production or smoking. These data reinforce the concept that some kind of airway remodeling occurs progressively in asthma. It is hoped, but not yet proven, that long-term anti-inflammatory medication will reduce the rate of decline.*
R. J. M.
Lange PL, Parner J, Vestbo J, et al: A 15-year follow-up study of ventilatory function in adults with asthma. **N Engl J Med** 339:1194-1200, 1998. ♦♦

Study Confirms Early Onset and High Severity of Peanut Allergy

PEANUT allergy appears to be increasing in frequency in Europe. The findings of 142 French patients with peanut allergy were reported, including standard oral provocation tests to determine the reactive dose of peanuts. The potential for reaction to peanut oil was assessed as well.

All patients were seen at two French allergy centers. Twenty-eight ➤➤

percent of all cases of food allergy seen at these centers were peanut allergy. Age was less than 1 year in 46% of patients, and less than 15 years in 93%. Forty percent of patients had atopic dermatitis and 37% had angioedema; less common clinical manifestations included asthma, anaphylactic shock, and digestive symptoms. About half of patients had isolated peanut allergy. In most patients, peanut allergy was clinically unsuspected.

Skin-prick testing and specific IgE testing both offered diagnostic sensitivity of greater than 90%. Eighty percent of patients had class 2 or higher specific IgE. On oral provocation testing, the total reactive dose was less than 100 mg in 25% of patients and between 100 mg and 1 g in 62.5%. No patient required a dose of higher than 7.1 g before showing a reaction; the threshold of peanut reactivity was significantly lower than that of egg reactivity. Of 62 patients undergoing oral provocation testing for peanut oil, 14 had positive results.

The findings confirm that peanut allergy is a severe food allergy of childhood onset. Skin-prick tests and blinded challenge studies confirm that residual allergenic proteins are present in peanut oil. Patients with peanut allergy may have continued exposure to allergen in the form of peanut oil or fats. This exposure may be responsible for persistent symptoms and may increase the risk of sensitization.

COMMENT: *This report supports the contention that peanut allergy tends to occur earlier in life than other food allergies, and the provocative dose for symptoms tends to be lower than for other food allergens. Double-blind, placebo-controlled oral provocation tests confirmed sensitivity to peanut oil in roughly one-fifth of patients with peanut allergy. Skin testing with peanut oil had poor predictive value.*
S. A. T.

Moneret-Vautrin DA, Rance F, Kanny G, et al: Food allergy to peanuts in France: evaluation of 142 observations. **Clin Exp Allergy** 28:1113-1119, 1998. ♦♦

Inhaled Salmeterol Can Mask Worsening Asthma

LONG-ACTING β-agonists have become a key part of asthma treatment. However, there is concern that such treatment may heighten the risk of more severe asthma by delaying recognition of increasing airway inflammation. This could be especially dangerous if patients used less corticosteroid as their symptom control improved.

The potential masking effects of salmeterol were examined in a placebo-controlled trial. The subjects were 13 asthma patients with an inhaled corticosteroid dosage of at least 1,500 μg/day. After a 1-week run-in period, the patients were randomly assigned to receive salmeterol dry powder, 50 μg twice daily via Diskhaler, or placebo. The corticosteroid dose was progressively reduced until the patients met criteria for an exacerbation, or until corticosteroid was completely withdrawn. After a 4-week stabilization period, the patients were crossed over to the alternative treatment. Response was assessed using symptom and peak expiratory flow (PEF) diaries and weekly spirometry, methacholine challenge, blood, and sputum measurements.

One week of salmeterol therapy significantly reduced β_2-agonist use, increased mean morning PEF, and increased FEV_1. It also reduced inhaled corticosteroid dose to a greater extent than placebo, 87% versus 69%. Exacerbations were preceded by increased sputum eosinophil counts, despite stable symptom status, FEV_1, and PEF. Sputum eosinophilia exceeded 10% before exacerbation in 5 patients during salmeterol therapy versus 2 patients during placebo.

In patients with asthma, regular salmeterol therapy may disguise progressive airway inflammation, thus delaying recognition of asthma exacerbations. The findings suggest that salmeterol may keep asthma symptoms and lung function under control until significant airway eosinophilia has developed. The authors urge caution in reducing inhaled corticosteroid therapy for asthmatic patients receiving long-acting β-agonists.

COMMENT: *The authors study the possibility that long-acting β-agonists may mask the signs of increasing airway inflammation and delay awareness of worsening asthma. In an attempt to decrease the possible long-term morbidity of inhaled steroids by adding long-acting bronchodilators, are we actually placing patients at risk? Conflicting data regarding this issue exist in the literature, and the jury is still out.*
J. M. P.

McIvor RA, Pizzichini E, Turner MO, et al: Potential masking effects of salmeterol on airway inflammation in asthma. **Am J Respir Crit Care Med** 158:924-930, 1998. ♦♦

Dust Mite Control Measures Don't Reduce Allergen Exposure

A meta-analysis of 23 randomized trials was performed to assess the effectiveness of measures to reduce exposure to house dust mite allergen in sensitized patients with asthma. The studies included a total of 113 patients in treatment groups and 117 patients in untreated control groups. The mite-control measures examined included chemical methods in 6 patients, physical methods in 13, and a combination of methods in 4. All studies used skin prick testing, bronchial provocation testing, or specific IgE antibody assays to confirm sensitivity to mites. The standardized effect size method--i.e., the difference in effect divided by the standard deviation of the measurements--was used to compare outcomes measured using different scales.

The percentage of patients improved was 36% in the treatment groups and 32% in the control groups, a nonsignificant difference. Standardized mean differences in outcomes were −0.06 for improvement in asthma ➤➤

symptoms and –0.03 for peak morning flow rate. For peak flow rate, this translated into a difference of –3 L/min. The population of mites was sucessfully reduced in 6 of 18 studies, but this did not improve the likelihood of clinical benefit. Neither did studies with longer follow-up times show better results.

Measures to reduce dust-mite exposure do not appear to be of any clinical benefit for sensitized asthma patients, the available evidence suggests. Currently used chemical and physical allergen-reducing techniques seem to be ineffective. The authors call for larger, more rigorous studies investigating the effectivness of other mite control techniques.

COMMENT: *Dust mite avoidance procedures are a fundamental part of treatment for patients with allergic rhinitis and asthma with mite sensitivity. This meta-analysis failed to document clinical improvement with these programs. Only four studies used both physical and chemical methods, which may explain the results. Further studies are indicated before we abandon the use of mite-reducing programs for our patients.*
M. S. B.
Gøtzsche PC, Hammarquist C, Burr M: House dust mite control measures in the management of asthma: meta-analysis. **BMJ** 317:1105-1110, 1998. ♦♦

WHO Presents Guidelines for Allergen Immunotherapy

THE World Health Organization has published consensus guidelines for allergen immunotherapy. This document reviews evidence demonstrating the effectiveness of allergen immunotherapy for patients with allergic rhinitis/conjunctivitis, allergic asthma, and allergic reactions from stinging insects. In appropriate cases-i.e., for patients with specific IgE antibodies to clinically relevant allergens--immunotherapy should be used in combination with other established treatments. It should be prescribed only by physicians with specialist training in allergy/immunology.

The quality of allergen vaccines is a key consideration; only allergens of known potency and shelf life should be used. With these vaccines, an optimal maintenance dose of 5 to 20 μg of major allergen per injection can be defined for specific allergens. Given the risk of anaphylaxis, allergen immunotherapy should only be given under the care of a trained physician. There is no consensus as to the ideal duration of immunotherapy, though a duration of 3 to 5 years is recommended on the basis of clinical response. It is hoped that the new guidelines will increase understanding of the science and underlying rationale of allergen immunotherapy and improve the safety of this approach.

COMMENT: *This extremely useful position paper outlines the definition of allergen immunotherapy and the data supporting it as an effective treatment for patients with allergic rhinitis, allergic asthma, and allergic reactions from stinging insects. The indications and guidelines for its administration, along with potential benefits and risks are covered lucidly and succinctly.*
E. J. B.
WHO Position Paper: Allergen immunotherapy: therapeutic vaccines for allergic diseases. **Allergy** 53 (suppl), 1998. ♦♦

Influenza Vaccine Can Be Safely Given to Patients with Egg Allergy

CURRENT recommendations for the use of influenza vaccine in patients with a history of egg allergy are confusing and based on limited scientific evidence. A multicenter clinical trial demonstrated the safety of a two-dose influenza vaccination protocol in egg-allergic patients. The two doses were given 30 minutes apart. The first was one-tenth of the age-appropriate recommended dose, and the second was nine-tenths of the recommended dose. All 83 patients with egg allergy studied tolerated the two-dose protocol with no significant allergic reactions. Just 5% had a positive skin test result to influenza vaccine.

Over 3 years, the level of egg protein contained in the Parke Davis vaccines used in the study varied from 0.02 to 1.2 μg/mL, according to inhibition enzyme-linked immunosorbent assay. Other preparations of influenza vaccine had much higher egg protein contents.

The two-dose protocol permits safe influenza vaccination of patients with egg allergy. Clinical use of this approach will depend on the variable egg protein content of available influenza vaccines.

COMMENT: *This is an important article, since the American Academy of Pediatrics still recommends skin testing before administration of influenza vaccine for children with severe egg allergy. The study shows that patients with egg allergy can receive influenza vaccine safely. Equally important is the fact that some brands of vaccine contain 100 times less egg protein (i.e., Parke-Davis).*
J. B.-M.
James JM, Zeiger RS, Lester MR, et al: Safe administration of influenza vaccine to patients with egg allergy. **J Pediatr** 133:624-628, 1998. ♦♦

Once-Daily Budesonide Reduces Risk of Slow Growth in Children

THIS study compared the short-term growth effects of two budesonide regimens in children with asthma. Twenty-four asthmatic children, aged 6 to 13 ➤➤

years, were randomized to receive budesonide in either a single daily dose of 800 μg or two daily doses of 400 μg. After 4 weeks, the patients were crossed over to the alternative regimen. Weekly measurements of lower leg growth were obtained using a knemometer. Serum markers of collagen turnover--including the carboxy terminal propeptide of type I procollagen and the amino terminal propeptide of type III procollagen-were measured as well.

The two treatment periods were similar in terms of peak expiratory flow rates, symptom scores, and β_2 agonist consumption. Mean lower leg growth rate was significantly reduced during the twice-daily dosing period, compared with once-daily dosing. Collagen turnover markers were also reduced with twice-daily dosing. Boys grew faster than girls during once-daily dosing, whereas there was no difference during twice-daily dosing.

For children with asthma, giving budesonide once daily in the morning may reduce the risk of steroid-associated growth suppression. Once-daily dosing also has a sparing effect on collagen turnover. Further studies are needed to determine whether once-daily dosing will be an effective regimen for children with severe asthma.

COMMENT: *Public attention has focused on growth rate in asthmatic children on inhaled corticosteroids, especially since the recent FDA recommendation for changes in the package inserts. It is of note that dose timing may be as important as total dose given per day. Longer-term studies using budesonide are needed to determine expected side effects of this agent in children.*
J. B.-M.

Hueck C, Wolthers OD, Kollerup G, et al: Adverse effects of inhaled budesonide (800 μg) on growth and collagen turnover in children with asthma: a double-blind comparison of once-daily versus twice-daily administration. **J Pediatr** 133:608-612, 1998. ♦♦

Medicinal Herbs May Cause Drug Interactions

MORE and more patients are using medicinal herbs, usually without their physician's knowledge. The author reviews some known interactions between medicinal herbs and drugs. Chamomile, used for its mild sedative effect, may cause allergic reactions, often in patients who also have ragweed allergy. *Echinacea*, used as an immunostimulant, has the potential for hepatotoxicity; it should not be used with other hepatotoxic compounds. Garlic--as well as feverfew, *Ginkgo*, ginger, and ginseng--may alter bleeding times, and should not be used by patients taking warfarin sodium. St. John's wort (*Hypericum perforatum*) is widely used for the treatment of depression. Since its mechanism of action is unclear, it should not be used with monoamine oxidase inhibitors or selective serotonin reuptake inhibitors. Valerian, used by patients with insomnia, may cause excessive sedation if taken in combination with barbiturates.

Digoxin levels may be affected by a number of different herbal medicinals, including kyushin, licorice, plantain, uzara root, hawthorn, and ginseng. Patients receiving anticonvulsant therapy should not take evening primrose oil or borage, because they may increase seizure risk; the Ayurvedic preparation Shankapulshpi may interfere with the levels and efficacy of phenytoin. There have been reports of coma in patients taking the sedative kava in interaction with alprazolam. Immunostimulating herbs such as *Echinacea* and *Astragalus* may interfere with the immunosuppressive effects of corticosteroids and cyclosporine. St. John's wort, saw palmetto, and other herbs containing tannic acid may inhibit iron absorption.

The author calls for more research to establish the safety and efficacy of increasingly used medicinal herbs, including studies of drug-herb interactions. Standardization and monitoring of these products are needed to overcome variations in quality and composition. Physicians should ask patients about herb use as part of the routine drug history.

COMMENT: *As part of an entire issue of this journal devoted to alternative medicine, this review summarizes selected clinical considerations about herbal remedies that are of concern in the care of patients, including those with allergic and immunologic disorders. Topics discussed include the cross-allergenicity between ragweed and medicinal chamomile, possible additive effects between ginseng and corticosteroids, photosensitivity reactions from St. John's wort, and the potential for antagonism of beneficial corticosteroid effects by Echinacea, Astragalus, licorice, alfalfa sprouts, vitamin E, and zinc.*
M. S. D.

Miller LG: Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. **Arch Intern Med** 158:220-2211, 1998. ♦♦

Zafirlukast Can Interact with Theophylline

THE new anti-inflammatory drug zafirlukast, recently approved for the treatment of asthma, has the potential for interaction with theophylline. The authors report a 15-year-old girl with asthma who was taking theophylline, 300 mg twice daily. Her theophylline levels had been stable at 11 μg/mL for years. However, when zafirlukast was added, theophylline levels jumped into the toxic range, 24 μg/mL. With each attempt to stop and restart theophylline at progressively lower doses, the patient's reaction became more toxic, with peak theophylline levels of 27 μg/mL.

This is a potentially serious drug interaction between zafirlukast and theophylline in a young asthma patient. The sharp rises in serum theophylline could result from zafirlukast-induced inhibition of cytochrome P450, which is responsible for theo- ➤➤

phylline metabolism. Serum theophylline levels should be monitored closely in patients receiving these two medications.

Comment: *The authors report a patient who developed toxic levels of theophylline when zafirlukast was added to theophylline therapy for asthma, possibly through inhibition of cytochrome P450 (CYP 1A2) by zafirlukast. The authors recommend that physicians evaluate serum theophylline levels closely when prescribing the two drugs in combination.*
M. S. D.

Katial RK, Stelzle RC, Bonner MW, et al: A drug interaction between zafirlukast and theophylline. **Arch Intern Med** 1581713-1715, 1998. ♦♦

New Questionnaire Measures Asthma-Specific Quality of Life in Low-Income Patients

THE Asthma Quality of Life Questionnaire (AQLQ) was developed to assess key domains of health-related quality of life germane to living with asthma: activity limitation, symptoms, emotional function, and environmental exposure. This instrument was tested for reliability and validity in a population-based sample of 112 low-income adults with asthma: 83 women and 29 men, 41% African-American, mean age 33 years.

The AQLQ showed high internal consistency and high reproducibility over a 2-week period. Validity was demonstrated by the finding of significant correlations between overall AQLQ score and indicators of disease severity, i.e., FEV_1 percentage of predicted and Asthma Disease Severity Scale score. The AQLQ score was also significantly correlated with the Physical Component and Mental Component Summaries of the Medical Outcomes Study Short-Form 36, a generic measure of health-related quality of life; Cantril's Self-Anchoring Ladder of Life Satisfaction, a global quality-of-life indicator; and the Health Utilities Index. Reliability and validity estimates were similar for Caucasian and African-American patients. African-Americans reported significantly lower health-related quality of life in each domain evaluated

The AQLQ appears to be a reliable and valid tool for measuring asthma-specific health-related quality of life in low-income patients with asthma. Scores on this instrument are significantly correlated with pulmonary function, symptoms, and other measures of health-related quality of life. Sex and race may have a significant impact on asthma-related quality of life.

Comment: *The authors attempt to demonstrate the validity of the AQLQ, developed by Juniper and colleagues, in a lower socioeconomic group. The time has come for patient-perceived quality of life to be an integral part of disease management and development of new treatment modalities. Juniper's AQLQ appears to be such a tool, with application across socioeconomic lines.*
J. N. P.

Leidy NK, Chan KS, Coughlin C: Is the asthma quality of life questionnaire a useful measure for low-income asthmatics? **Am J Respir Crit Care Med** 158:1082-1090, 1998. ♦♦

Inhaled Steroids Are Not Associated with Reduced Bone Mineral Density

NO studies have specifically examined the effects of inhaled steroid therapy on bone mineral density (BMD) in men. This study compared BMD in men and women with asthma or chronic obstructive pulmonary disease (COPD) who were or were not taking inhaled steroids. One hundred forty-four patients with reversible airflow obstruction were matched for age to 212 controls. All patients underwent measurement of bone mineral density. Disease severity and lifestyle factor were assessed as well.

Women with airflow obstruction who were taking inhaled steroids had a greater body mass index and a greater percentage of body fat than controls. Total-body and spine BMD were significantly reduced in both premenopausal and postmenopausal patients. Male patients had lower BMD than controls. Inhaled steroid use was associated with reduced BMD at the spine but not the hip. However, the relationship with spine BMD was nonsignificant in a multiple regression model including dietary calcium intake. Cigarette smoking was linked to reduced BMD at the hip.

This study finds that BMD is reduced in men with asthma and/or COPD, regardless of whether they are receiving inhaled steroids. Dietary and lifestyle factors, such as calcium intake and smoking, play a significant role. For women with airflow obstruction-even those receiving steroids-BMD is very similar to control levels.

Comment: *Intuitively, long-term inhaled corticosteroid use should result in accelerated loss of BMD. However, reports in the literature have been conflicting. This relatively small epidemiologic study from Hong Kong failed to convincingly link inhaled corticosteroids to a lower BMD. Interestingly, men with chronic obstructive pulmonary disease or asthma had lower BMD than controls, independent of corticosteroid exposure.*
S. A. T.

Lau EMC, Li M, Woo J, Lai C: Bone mineral density and body composition in patients with airflow obstruction: the role of inhaled corticosteroid therapy, disease and lifestyle. **Clin Exp Allergy** 28:1066-1071, 1998. ♦♦

Has Reduced Aspirin Use Led to Increased Prevalence of Childhood Asthma?

STARTING in the early 1980s, when pediatric aspirin use was linked to Reye's syndrome, the use of aspirin by children decreased. At the same time, the rate of increase in the prevalence of asthma in children accelerated. The authors suggest that decreasing aspirin use in children may be a factor in the increasing prevalence of asthma.

Reye's syndrome is associated with use of aspirin during febrile respiratory infections in children. As these infections resolve, prostaglandin E_2 is produced through the activity of cyclo-oxygenase-2 (COX-2). By blocking the COX-2 pathway of arachidonic acid metabolism, aspirin inhibits production of PGE_2, whereas acetaminophen does not have this effect. Prostaglandin E_2 affects the balance between the TH1 and TH2 cytokines. In children with a genetic predisposition to TH2-type immune responses, substitution of acetaminophen for aspirin may cause a shift in the TH1:TH2 balance, thus favoring the development of allergic sensitization and asthma.

Based on epidemiologic, biologic, and pharmacologic data, the authors suggest that the decreased use of aspirin in children may have contributed to the increasing prevalence of childhood asthma. Further study is needed to evaluate the role of this and other potential factors in the alarming increase in asthma among children.

COMMENT: *This article addresses the highly publicized, important issue of the increasing prevalence of childhood asthma. With increased understanding of the relationship of Reye's syndrome to aspirin consumption, the use of aspirin in pediatric populations has dramatically decreased. The authors hypothesize that this trend has led to increased allergic sensitization in asthma through the generation of COX-2-mediated PGE_2. Since PGE_2 can promote the "allergic" TH_2 phenotype in cytokine production, this is an intriguing hypothesis. Further studies of this phenomenon will be required.*
T. M.

Varner AE, Busse WW, Lemanske RF Jr: Hypothesis: decreased use of pediatric aspirin has contributed to the increasing prevalence of childhood asthma. **Ann Allergy Asthma Immunol** 81:347-351, 1998. ♦♦

Acute *Chlamydia* Infection May Lead to Chronic Asthma

THE possibility that the common respiratory pathogen *Chlamydia pneumoniae* could induce asthma was investigated. The study included 163 patients, aged 15 years or older, seeing their family physician for acute wheezing or chronic asthma. Fifty-five percent of the patients were women; the average age was 43 years. All patients underwent serologic testing for *C. pneumoniae* infection, while a subgroup underwent nasopharyngeal cultures. Ten patients were having their first episode of wheezing. The remaining 153 reported previous episodes of wheezing, and thus were classified as having chronic asthma.

Chlamydia pneumoniae infection was documented in 12% of patients overall. Ten of these twenty patients had de novo wheezing and ten had chronic asthma. Five of the *Chlamydia*-positive patients with de novo wheezing went on to develop chronic asthma, while another developed chronic bronchitis. For the *Chlamydia*-positive patients in the chronic asthma group, the serologic findings suggested chronic rather than acute *C. pneumoniae* infection.

In this study, one-half of patients with a first episode of wheezing and acute *C. pneumoniae* infection went on to develop chronic asthma. The authors recommend serologic testing for *C. pneumoniae* in patients with asthma of recent onset, as antimicrobial therapy may be beneficial. For patients with a previous diagnosis of chronic asthma, the possibility of chronic *C. pneumoniae* infection should be investigated.

COMMENT: *In this study 20 of 163 primary care-based outpatient adolescents and adults with acute wheezing or chronic asthma were diagnosed with* C. pneumoniae *infection. Five of ten patients with new-onset wheezing and acute infection with* C. pneumoniae *developed chronic asthma. Since* C. pneumoniae *infections in individuals without asthma are common, the significance of these serologic abnormalities require confirmation in larger populations. Nevertheless, the findings suggest that* C. pneumoniae *infection, which is responsive to antibiotic therapy, may be associated with acute and chronic asthma.*
T. M.

Hahn DL, McDonald BS: Can acute Chlamydia pneumoniae respiratory tract infection initiate chronic asthma? **Ann Allergy Asthma Immunol** 81:339-344, 1998. ♦♦

Children Show Late Asthmatic Responses to Exercise After Allergen Exposure

PREVIOUS studies in adults have reported that asthma patients may show delayed asthmatic responses to exercise after a late response to allergen. The occurrence of such responses was evaluated in 17 children with asthma who had late asthmatic responses to inhaled allergen. The children performed exercise challenge tests 2 days before and 2 days after an allergen challenge. Factors associated with late responses to exercise were analyzed as well.

All patients had isolated early asthmatic responses to the pre-allergen exercise test. The post-allergen exercise test produced a dual response--i.e., early and late asthmatic responses--in 7 children. The remain- ➤➤

ing 10 patients had early responses only. The methacholine dose shift caused by allergen challenge was significantly greater in the children with a dual response. All other aspects of the airway response to allergen were similar between groups.

Some children with asthma who have late asthmatic responses to allergen challenge may also show a late response to exercise. This dual response is related to the extent of increased methacholine sensitivity caused by allergen challenge, rather than to the baseline or post-allergen methacholine PC_{20}.

Comment: *This article expands our understanding of the enhancing effect of aeroallergen exposure on bronchial hyperresponsiveness. While there have been previous case reports of adults who have developed late asthmatic responses after exercise performed after allergen challenge, this is the first study in children. The authors found that 7 of 17 children with mild to moderate controlled asthma displayed a dual response to exercise 2 days after allergen challenge. The remaining children displayed isolated early asthmatic responses. These are extremely important observations, since the presence of a dual response to a challenge in the past has been associated with an immunologic mechanism.*
T. M.
Koh YY, Jeong JH, Jin SM, et al: The occurrence of late asthmatic response to exercise after allergen challenge. **Ann Allergy Asthma Immunol** 81:366-372, 1998. ♦♦

Low Levels of Ozone Do Not Enhance Airway Response to Allergen

In a previous study, the authors found that exposure to the common air pollutant ozone, 120 ppb, enhanced the response to allergen in most patients with mild allergic asthma. However, other research groups did not replicate this finding. The authors performed a larger study, using a larger exposure chamber to better control ozone levels.

The prospective, randomized trial included 15 patients with mild allergic asthma. There were 9 men and 6 women, mean age 33 years and mean FEV_1 3.4 L. On separate days, in random order, the patients were exposed to filtered air and ozone. The mean ozone level was 120 ppb, with a range of only 110 to 130 ppb, much narrower than in the previous study. After each 1 hr exposure, the patients underwent allergen challenge with either grass pollen or ragweed extract. The allergen concentration causing a 15% fall in FEV_1 (PC_{15}) was compared between exposures.

The allergen PC_{15} was not significantly different after ozone exposure versus clean air exposure. This value was lower after ozone exposure in 5 patients, but increased in 6 and unchanged in 4.

Using better controls than in their previous study, the authors find no effect of ozone exposure on subsequent airway responsiveness to allergen among patients with mild allergic asthma. Further research, including additional variables--such as fluctuating versus constant ozone levels and patients who are high versus low ozone responders--may help to clarify the interactions between ozone and allergen in patients with asthma.

Comment: *While exposure to low levels of nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) have been convincingly shown to increase airway hyperresponsiveness to inhaled allergen in allergic asthmatics, the effects of ozone have been less clear. This well-controlled and relatively large study suggests that low-level ozone exposure does not potentiate the airway response to inhaled allergen.*
S. A. T.
Hanania NA, Tarlo SM, Silverman F, et al: Effect of exposure to low levels of ozone on the response to inhaled allergen in allergic asthmatic patients. **Chest** 114:752-756, 1998. ♦♦

High-Dose IV Immunoglobulin Reduces Steroid Requirement in Severe Asthma

Alternative treatments are needed for patients with severe, steroid-dependent asthma. A few studies have suggested that IV immunoglobulin (IVIg) may be helpful in this situation.

In an open-label trial, 11 adolescent or adult patients with severe, steroid dependent asthma were treated with IVIg. All patients required an oral steroid dose of at least 0.25 mg/kg/day. The patients received 6 months of therapy with human IVIg, at a dose of 2 g/kg. Treatment was given every 4 weeks, for a total of 7 infusions. The results were evaluated in terms of bone density, pulmonary function, airway reactivity, and steroid requirement.

With IVIg, oral steroid requirement decreased by more than 50% in 9 of the 11 patients, and by 40% or greater in all patients. Average daily steroid dose decreased from approximately 32 to 6 mg. At the same time, pulmonary function improved significantly; mean prebronchodilator FEV_1 improved from 60% to 68%. Morning peak expiratory flow rate improved from 71% to 86%. Daily symptom scores and bone mineral density improved significantly as well. The treatment had no effect on responses to methacholine challenge.

This study adds to the evidence that IVIg may be a useful therapy for patients with severe, steroid-dependent asthma. The mechanism of this effect remains unclear--there are many potential targets for IVIg. With further study, IVIg may help to improve pulmonary function and symptoms while reducing steroid requirements in steroid-dependent asthma.

Comment: *In this small, uncontrolled study, high doses of IVIg (2 g/kg) were beneficial for a subset of patients with severe, steroid-dependent asthma. The mechanism of action of this treatment is of primary importance. It is hoped that through future controlled* ➤➤

studies we will be able to learn more about this mechanism.
J. B.-M.
Landwehr LP, Jeppson JD, Katlan MG, et al: Benefits of high-dose IV immunoglobulin in patients with severe steroid-dependent asthma. **Chest** 114:1349-1356, 1998. ♦♦

Activated Eosinophils May Be Involved in Churg-Strauss Syndrome

IT has been suggested that reduced steroid dosage or withdrawal in patients with asthma may lead to Churg-Strauss syndrome (CSS). This research letter describes a case of CSS in a 37-year-old woman with asthma who stopped taking her high-dose inhaled steroids during pregnancy. She was admitted with worsening dyspnea and eosinophilia. Her respiratory symptoms gradually improved with nebulized β_2-agonists and high-dose inhaled steroids. When the patient developed a severe right temporal headache, Doppler scanning showed a microaneurysm of the temporal artery. Temporal artery biopsy revealed panarteritis with massive perivascular and intravascular eosinophil infiltration, along with fibrinoid necrosis, eosinophil granulomata of the arterial walls, and thrombosis of the arterial lumen. The mother and child both had good outcomes; the mother had no additional signs of systemic vasculitis.

This case adds to the evidence that activated eosinophils may play a pathogenetic role in CSS. A previous report described the necropsy finding of eosinophil cationic protein (ECP) in a patient with CSS and heart involvement. In the current case, serum ECP concentration was elevated before treatment and normalized thereafter. Measuring serum ECP might be a useful means of monitoring disease activity in CSS.

COMMENT: *Churg-Strauss Syndrome has been observed after steroid withdrawal in asthmatic patients. This exemplary case in a pregnant patient sheds light on the pathogenetic mechanism, i.e., activated eosinophils and their cytotoxic products such as ECP. Serum ECP levels may be a useful way to diagnose and monitor CSS.*
E. J. B.
Priori R, Tomassini M, Magrini L, et al: Churg-Strauss syndrome during pregnancy after steroid withdrawal. **Lancet** 352:1599-1600, 1998. ♦♦

Pet Allergens Build Up Quickly in Public Places

A study of mattresses in furniture stores was performed to analyze the accumulation of animal danders in pet-free public places. Dust samples were obtained from factory-new mattresses and from display mattresses used by customers. Concentrations of cat, dog, and horse allergens were measured by enzyme-linked immunosorbent assay and countercurrent electron immunophoresis.

Eighty-eight percent of the factory-new mattresses already showed detectable levels of cat and/or dog allergen, though in very low concentrations. Even though some of the mattresses were stuffed with horsehair, none showed horse allergen. All samples from mattresses tried by customers showed cat and dog allergens; the longer the mattresses had been on display, the higher the allergen concentrations. In busy stores, it only took 3 weeks before allergen concentrations were similar to those in homes in which pets had previously been kept, or even the lower end of the range for homes with current pets.

The study shows that animal allergens can accumulate very quickly in pet-free public places. Most likely, the allergens are deposited by people who have been in direct or indirect contact with pets. A similar pattern of allergen spread is likely operative in other public settings, such as day-care centers and schools. New approaches are needed to reducing exposure to pet allergens, especially among allergic children who are sensitized to pet fur.

COMMENT: *Distribution of allergens from furred animals to pet-free public places is likely to occur by deposition from people who have contact with pets. The accumulation is significant and occurs in a short period of time.*
E. J. B.
Egmar A-C, Almqvist C, Emenius G, et al: Deposition of cat (Fel d 1), dog (Can f 1), and horse allergen over time in public environments: a model of dispersion. **Allergy** 53:957-961, 1998. ♦♦

Cereal Flour Can Be Occupational Allergen in Woodworkers

OCCUPATIONAL sensitization of wood industry workers to an allergen previous associated with baker's asthma is reported. The authors describe 3 workers in a wood factory who developed allergic symptoms during the work week. The diagnostic workup included skin-prick testing and CAP to cereal flours, which were used to improve the properties of the glue used in making veneer panels.

All 3 workers were sensitized to cereal flours, according to the results of skin prick testing and CAP. Immunoglobulin E immunoblotting identified only low-molecular weight proteins under 20 kDa. These proteins belonged to the α-amylase inhibitor family, which are one of the major allergens present in rye, barley, and wheat. After changing jobs, all 3 patients became asymptomatic, even though they remain in contact with woods, wood dust, and chemicals such as formaldehyde. All 3 have required treatment when entering areas in which the cereal flour-containing glues are used. ➤➤

Cereal flour allergens may be emerging as a cause of occupational sensitization in the wood industry. This could be an easily misdiagnosed cause of occupational asthma. Preliminary study suggests a prevalence similar to that of baker's asthma, i.e., 5% to 30% of exposed workers.

Comment: *Although cereal α-amylase inhibitors have been previously described as important allergens in baker's asthma, this is the first report that such agents can be important occupational allergens in wood industry workers. These cereal allergens are introduced when cereal flours are added to urea-formaldehyde resin that is used as a glue for wood veneer products.*
M. S. D.
López-Rico R, Moneo I, Rico A, et al: Cereal α-amylase inhibitors cause occupational sensitization in the wood industry. **Clin Exp Allergy** 28:1286-1991, 1998. ♦♦

Can Smaller Peptides Reduce Sensitization to Cow's Milk?

In children with allergy to cow's milk, milk hydrolysates always have some residual antigenicity and allergenicity, depending in part on the molecular weight of the remaining peptides. An in vitro study was done to define the lowest molecular weight of peptides capable of causing skin reactions and binding IgE antibodies.

Five children with allergy to cow's milk underwent skin-prick testing with an ultrafiltrated whey hydrolysate and its fractions. Radioallergosorbent inhibition tests were carried out using the patients' serum. Chromatography identified 7 fractions with molecular weights of 15,000 to 125 Da. Peptides of greater than 2,600 Da always caused a positive skin reaction and inhibited IgE binding. In contrast, peptides of smaller than 1,400 Da caused no skin reactions, but still inhibited IgE binding somewhat.

Sensitization to cow's milk appears to occur through transfer in breast milk of antigens digested by the mother. Partially digested material appears to be antigenically active, and may cause sensitization even after intestinal absorption and transfer to the fetus. Small peptides of 970 to 1,400 Da might be useful for children with cow's milk allergy who react to milk hydrolysates, and may even induce tolerance.

Comment: *Formulas of cow's milk hydrolysate have been developed to eliminate the allergenicity of these products, but residual antigenicity and allergenicity have been reported even in extensively hydrolyzed formulas. This study concludes that peptides of less than 1,400 Da do not elicit skin test reactivity, and that the minimal molecular mass for IgE binding is situated between 1,400 and 970 Da. The authors suggest that such peptides may be used to develop a safe formula for patients reacting to milk hydrolysates.*
M. S. D.
Van Hoeyveld EM, Escalona-Monge M, De Swert LFA, Stevens EAM: Allergenic and antigenic activity of peptide fragments in a whey hydrolysate formula. **Clin Exp Allergy** 28:1131-1137, 1998. ♦♦

New Guidelines for Prevention of Respiratory Syncytial Virus Infection

THE monoclonal antibody preparation palivizumab was recently approved for use in the prevention of respiratory syncytial virus (RSV) in high-risk infants and children. A large randomized, placebo-controlled trial found that palivizumab reduced the risk of RSV-attributable hospitalization in high-risk patients by 55%. This treatment is especially valuable in patients with chronic lung disease (CLD) (previously called bronchopulmonary dysplasia) and for premature infants without CLD.

Respiratory syncytial virus immune globulin intravenous (RSV-IGIV) was previously proven effective in the prevention of severe RSV lower respiratory disease in high-risk patients. However, palivizumab is preferred for use in most patients, for a number of reasons: it is given IM rather than IV, it does not require delay in measles-mumps-rubella or varicella vaccination, and it does not carry the complications of human immune globulin products. However, RSV-IGIV can protect against other respiratory viruses as well, and may be indicated for children receiving IV immune globulin therapy because of immunodeficiency conditions. Prophylactic RSV-IGIV may be considered for premature infants who are to be discharged during the RSV season. There are limited cost data on RSV-IGIV, and none on palivizumab.

Prophylaxis against RSV is indicated for CLD patients less than 2 years old who have received medical therapy for CLD within 6 months before RSV season, and for infants born at or before 32 weeks' gestation who do not have CLD. Neither treatment should be used in patients with congenital heart disease. Palivizumab is safe, with no higher rate of adverse events than placebo.

Comment: *A monoclonal antibody RSV preparation is now available for premature babies and those with chronic lung disease (formally designated bronchopulmonary dysplasia). This is the second antibody preparation available for RSV treatment. The naming of these agents is unique and very specific:*
"mab," monoclonal antibody.
"u," human source (versus "o," mouse, or "zi," combined).
"viz," virus (versus "cir," cardiovascular, or "tum," tumor specific).
"pali," drug specific naming.
J. B.-M.
American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and ➤➤

Newborn: Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IGIV. **Pediatrics** 102:1211-1216, 1998. ♦♦

Experts Review Knowledge of Nocturnal Asthma

THE authors present the findings of a National Heart, Lung, and Blood Institute workshop held to review current understanding of nocturnal asthma (NA). The term *nocturnal asthma* refers to asthma symptoms, need for asthma medication, airway responsiveness, or worsening of lung function related to sleep and/or circadian events. Several lines of evidence suggest that circadian factors and sleep play a role in asthma. Patients with asthma have reduced sleep efficiency, which has consequences for daytime performance; they may also have increased morbidity and mortality. During sleep, patients with NA show increased airway resistance and reduced volume of the hyperinflated lungs. Gastrointestinal function also varies during sleep, though the contribution of gastroesophageal reflux to NA remains unclear. Nonspecific airway responsiveness appears to be increased at night, particularly in patients with nocturnal increases in airway obstruction. Late asthmatic reactions to allergen challenge are also increased at night, further increasing bronchial responsiveness. Studies of the role of inflammation in NA suggest that circadian activation of inflammatory cells may occur in affected patients, and play a significant role in airflow limitation.

The goal of chronotherapy is to synchronize the patient's medication levels according to the times of need. This is sometimes achieved through sustained-release formulas, though special drug-delivery systems are more dependable. Sustained-release theophylline can be given to achieve a rising blood drug level as airway obstruction is increasing. Theophylline can also work in conjunction with inhaled corticosteroid. Other agents used in chronotherapy include sustained-release β-agonists and the long-acting inhaled β_2-agonists salmeterol and formoterol. Chronotherapeutic dosing of oral and inhaled steroids is efficacious as well. Leukotriene-active drugs, especially zileuton, have been shown to reduce symptoms and improve lung function in patients with NA. The authors identify some key areas for future research, including the immunology of the lung, the role of inflammation in NA, the daytime consequences of NA, and the physiology of sleep-associated changes in upper-airway caliber and lower-airway responses.

COMMENT: *This summary briefly reviews current knowledge regarding nocturnal asthma while highlighting the gaps in our understanding. Direction for future research is also outlined.*
J. M. P.

Martin RJ, Banks-Schlegel S: Chronobiology of asthma. **Am J Respir Crit Care Med** 158:1002-1007, 1998. ♦♦

Molds in the Home Linked to Variable Lung Function in Atopic Children

FEW studies have objectively examined the effects of living in a damp home on lung function and atopy. As part of a larger study of the effects of air pollution on children with asthma, the authors identified 1,614 children with asthma from 10 European countries. Home dampness was assessed through parental reports of moisture stains and molds. Linear regression models were used to evaluate associations between dampness and peak expiratory flow (PEF) variability, respiratory symptom frequency, and the use of relief medications. Skin-prick testing was performed to determine the presence of atopy.

Among children with atopy, the presence of reported molds in the home was positively related to PEF variability. The presence of moisture stains did not affect this lung function parameter. The presence of molds and moisture stains were both associated with an increased period prevalence of cough and upper respiratory symptoms.

This study links reported molds in the home to increased PEF variability among atopic children. Living in a damp home also seems to be associated with increased airway lability among children with chronic respiratory symptoms, especially for atopic children. An editorial accompanying this study underscores the need to develop reliable measures of exposure to mold allergens.

COMMENT: *Previous studies have reported strong associations between reported home dampness and respiratory symptoms, but only a weak, insignificant relationship between home dampness and pulmonary function. This study demonstrated that reported home dampness and the presence of molds had a high correlation with increased PEF variability in children having symptoms of asthma and chronic cough, a correlation that was greatest in atopic children. Although the study did not directly measure levels of house dust mites and molds that may be associated with dampness, the findings lend further support to recommendations to reduce indoor humidity levels in homes.*
M. S. D.
Andriessen JW, Brunekreef B, Roemer W: Home dampness and respiratory health status in European children. **Clin Exp Allergy** 28:1191-1200, 1998. ♦♦

Chiropractic Is of No Benefit for Childhood Asthma

A randomized, controlled trial assessed the value of spinal manipulation for children with mild to moderate asthma. The study included 91 children who had had asthma for longer than 1 year and were using a bronchodilator at least three times weekly. As determined by chiropractic examination, each child had vertebral subluxation on palpation. Baseline assessments included measurement of peak expiratory flow, a symptom diary, methacholine challenge, and the Pediatric Asthma Quality of Life Questionnaire. All children received 4 months of regular chiropractic treatment, consisting of active or simulated spinal manipulation. All children continued on their previous medication throughout the study. The main study outcome was the change in morning peak expiratory flow at 2 and 4 months.

There were 80 evaluable patients. Both the active- and sham-treatment groups showed small increases in morning and evening peak expiratory flow, i.e., 7 to 12 L/min. However, the two groups were similar in degree of change from baseline at both assessment points. Asthma symptoms and β-agonist use decreased to a similar extent in both groups, while quality of life improved. The results of spirometry and methacholine challenge testing did not change significantly in either group.

This scientific trial does not confirm anecdotal reports that chiropractic spinal manipulation is beneficial in childhood asthma. Usual medical care produces improvements in symptoms and quality of life while reducing the need for inhaled β-agonists, with or without chiropractic care. Neither treatment produces significant changes in objective measures of airway function.

COMMENT: *This study, funded by grants from four chiropractic sources, shows that collaborative research is possible between alternative and traditional providers, using scientific (randomized, controlled, and blinded) protocols. Children (7 to 16 years old) with asthma were treated for 4 months with active or sham chiropractic treatments in addition to stable medication regimens. Active chiropractic treatment was no more effective than sham treatment on symptoms, peak flows, FEV_1, β-agonist use, and methacholine challenge reactivity. Chiropractic care may have some benefit for some musculoskeletal conditions, but apparently not for asthma. An accompanying editorial states, "it is currently inappropriate to consider chiropractic as a broad-based alternative to traditional medical care. . . there appears to be little evidence to support the value of spinal manipulation for non-musculoskeletal conditions."*

R. J. M.

Balon J, Aker PD, Crowther ER, et al: A comparison of active and stimulated chiropractic manipulation as adjunctive treatment for childhood asthma. **N Engl J Med** 339:1013-1020, 1998. ◆◆

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