AllergyWatch®

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

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Wanted: Pied Piper!

RAT allergen is a recognized cause of IgE-mediated occupational allergies, but little is known about its contribution to allergic disease in the home. Previous data from the National Cooperative Inner-City Asthma Study (NCICAS) suggest a 19% rate of sensitization to rat allergen among inner-city children. The prevalence of rat allergen exposure and sensitization among inner-city children was assessed, including associations with asthma morbidity.

A new enzyme-linked immunosorbent assay was used to measure levels of the rat allergen Rat n 1 in dust samples from homes included in NCICAS. Rat allergen was detected in 21% of bedrooms sampled, 27% of living rooms/TV rooms, and 19% of kitchens. Of the total 645 homes for which dust samples were available, 33% had measurable Rat n 1 in at least one room. Homes with reported rat or mouse infestation were three times more likely to have detectable rat or mouse allergen than homes not reporting infestation. Homes with evidence of mouse infestation were more likely to have detectable rat allergen as well.

Asthma morbidity was assessed in 489 children--mean age 6.2 years and 63% boys--from the original NCICAS sample. Risk factors included a family history of asthma in 42% of patients, smoking in the home in 58%, and inadequate social support in 43%. Twenty-one percent of the children were sensitized to rat allergen, with similar rates for homes with vs without detectable bedroom or living/TV room exposure. Twenty-two children were both sensitized to rat and exposed to rat allergen in the bedroom. Children in this group experienced significantly elevated asthma morbidity, including more hospitalizations, more unscheduled medical visits, and more days with asthma-related activity limitations.

One-third of inner-city homes have detectable rat allergen, and one-fifth of children living in these homes are sensitized to rat allergen. Rat allergen is not as prevalent as mouse allergen, but is associated with greater asthma morbidity among sensitized children. Rat allergen is more likely to be present in inner-➤➤

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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 Internal Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal

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city homes with evidence of rodent infestation; other home characteristics associated with the presence of rat allergen remain unclear.

COMMENT: *Using dust samples collected from inner-city homes in the NCICAS, these researchers found detectable rat allergen in one-third of the homes. Although only 21% of the children were sensitized to rat allergen, these children had significantly increased morbidity because of their asthma. This had not been found in previous analyses of mouse antigen, in spite of the greater prevalence of mouse allergen in the inner-city homes. The significant correlation between rat exposure and increased asthma morbidity provides an additional reason to establish rat-control measures in inner-city neighborhoods. Where's the Pied Piper when you need him?*
S. M. F.

Perry T, Matsui E, Merriman B, et al: The prevalence of rat allergen in inner-city homes and its relationship to sensitization and asthma morbidity. **J Allergy Clin Immunol** 112:346-352, 2003. ♦♦

Formoterol 24 µg bid Linked to Serious Asthma Attacks

THE U.S. Food and Drug Administration (FDA) has approved formoterol at a dose of 12 µg bid for use in the treatment of asthma. This report reviews data suggesting an increased rate of serious asthma exacerbations associated with the use of a 24 µg bid dose of formoterol.

The analysis included three randomized, placebo-controlled trials evaluating multiple doses of formoterol. A total of 541 adult or adolescent patients participated in two 12-week trials; 554 children, aged 5 to 12 years, took part in a 1-year trial. The three studies had similar dropout rates.

In all three trials, the rate of serious asthma exacerbations was significantly higher in patients assigned to formoterol 24 µg bid than in those taking placebo, albuterol, or formoterol 12 µg bid. In patients taking the higher dose of formoterol, rates of serious exacerbations ranged from 3.0% to 6.4%, with the highest rate occurring in the pediatric trial. In all three studies, both doses of formoterol were superior to placebo in improving FEV_1. In this outcome, the 24 µg bid dose offered only a marginal advantage over formoterol 12 µg bid.

These trials suggest a consistently elevated frequency of serious asthma exacerbations in adults and children taking formoterol 24 µg bid. Regular use of long-acting inhaled β-agonists may increase the risk of such exacerbations via desensitization of the β-receptor. A placebo-controlled, postmarketing study of formoterol 24 µg bid is being performed to clarify the safety concerns involved.

COMMENT: *Authored by the FDA-employed physicians who reviewed the new drug application leading to formoterol's approval for use at a dose of 12 µg bid, this report analyzes data from three pivotal formoterol studies. In each study, the incidence of serious asthma exacerbations was higher among subjects treated with 24 µg bid. The authors imply that this higher dose may not be as safe as the currently approved dose. Additional trials are in progress and should help to clarify this important issue.*
S. A. T.

Mann M, Chowdhury B, Sullivan E, et al: Serious asthma exacerbations in asthmatics treated with high-dose formoterol. **Chest** 124:70-74, 2003. ♦♦

Immunotherapy with Adjuvant MPL Induces Allergen-Specific IgG Antibodies

THE mechanisms of allergen-specific immunotherapy for IgE-mediated allergies remain uncertain; there is ongoing debate as to the role of treatment-induced IgG antibodies. Previous studies have suggested that ➤➤

using monophosphoryl lipid A (MPL) together with immunotherapy yields a Th1-skewed immune response with enhanced IgG responses. Responses to grass pollen-specific immunotherapy with an MPL-adjuvanted vaccine were assessed, including IgE, IgG, and IgM responses.

The study included two groups of patients receiving preseasonal grass pollen immunotherapy: one group received grass pollen extract containing the Th1-driving adjuvant MPL, while the other received placebo. The recombinant timothy grass pollen allergens rPh1 p 1, rPh1 p 2, and rPh1 p 5 were used to assess immune responses to specific allergen molecules. Most of the patients receiving MPL showed strong induction of IgG_1 and/or IgG_4 responses to natural timothy grass pollen extract, as well as to rPhl p 5. No strong rPh1 p 1- or rPh1 p 2-specific responses occurred.

Induction of allergen-specific IgG_1 and IgG_4 was accompanied by a good clinical response to immunotherapy. The changes in allergen-specific IgG_4 and IgG_1 responses were comparable. During pollen season, patients in the active treatment group showed significant reduction of the seasonal boost in IgE production. In in vitro experiments, allergen-dependent basophil histamine release was significantly inhibited in sera from patients with treatment-induced IgG antibodies.

Immunotherapy with grass pollen extract containing adjuvant MPL leads to the production of allergen-specific IgG antibodies and a good clinical response. These antibodies may effectively inhibit immediate allergen-induced reactions, then block systemic increases in IgE during allergen season. The strongest induction of IgG antibodies appears to occur against the rPh1 p 5 molecule.

COMMENT: *The "blocking antibody" concept was originally proposed decades ago as an attractive hypothesis for explaining how immunotherapy works. This concept has been overshadowed significantly in the past few years as our understanding of T cells and their cytokines has increased. However, immunotherapy-induced changes in allergen-specific IgG have re-emerged as an important concept. Using preseasonal injections of grass pollen vaccine containing MPL adjuvant, Mothes and colleagues report striking correlations between these IgG antibodies and clinical efficacy.*
S. A. T.

Mothes N, Heinzkill M, Drachenberg KJ, et al: Allergen-specific immunotherapy with a monophosphoryl lipid A-adjuvanted vaccine: reduced seasonally boosted immunoglobulin E production and inhibition of basophil histamine release by therapy-induced blocking antibodies. **Clin Exp Allergy** 33:1198-1208. ♦♦

Influenza Vaccination Doesn't Reduce AOM Risk in Young Children

PREVIOUS studies, mainly in children over 2 years old, have suggested that influenza vaccination reduces the risk of acute otitis media (AOM). This study looked at the effects of influenza vaccine on AOM risk in infants and younger children.

During the 1999-2000 and 2000-01 seasons, a total of 786 children aged 6 to 24 months were randomized in 2:1 ratio to receive inactivated trivalent influenza vaccine or placebo. Depending on the specific strain involved, seroconversion rates in 66 vaccinated children ranged from 88.6% to 96.8%.

Efficacy in the prevention of culture-confirmed influenza was 66% during the 1999-2000 season and -7% in the 2000-01 season. Influenza attack rates were 15.9% and 3.3%, respectively. In both seasons, influenza vaccination had no significant effect on the percentage of children developing AOM: about 30% in the first season and 50% in the second season. The overall difference in proportion of vaccinated vs placebo-treated children developing AOM was only 3.0%. The two groups were also similar in the proportions of children developing AOM within 1 week after diagnosis of influenza and in the number of days with middle-ear effusion.

Influenza vaccination does not appear to reduce the overall risk of AOM in healthy children aged 6 to 24 months. Health care resource utilization is also unaffected. These data suggest that the efficacy of vaccination against serologically confirmed influenza is only 31% to 45%, better in children with prevaccination titers of 1:10 or greater.

COMMENT: *Life and medical practice would be less stressful, but very boring, if things always worked as we expect. Thus, not infrequently, knowledge we practitioners hold dear is shown to be false. This study does not demonstrate a reduction in AOM in infants aged 6 to 24 months who have been immunized with influenza vaccine. The vaccine is more effective in children older than 36 months and reduces influenza, but not AOM, in children younger than 24 months. Questions need to be answered, but for now give the vaccine and know you will reduce hospitalizations in younger children and may reduce AOM in older children. At least, I think we know this now.*
D. K. L.

Hoberman A, Greenberg DP, Paradise JL, et al: Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomized controlled trial.
JAMA 290:1608-1616, 2003. ♦♦

Histologic Study Shows Remodeling, But Not Inflammation, in Children with Severe Asthma

FEW studies have described the pathologic features of severe, steroid-dependent asthma in children. The clinical, pulmonary, and endobronchial biopsy findings in a series of 6 children with severe, uncontrolled asthma are reported.

The children were evaluated at a referral center because of severe, persistent asthma that had not responded to aggressive treatment, including long-term oral and high-dose inhaled glucocorticoids. The children were 4 girls and 2 boys, 9 to 17 years old. All under-➤➤

went bronchoscopy to exclude other respiratory diseases and/or inflammation.

In all 6 children, biopsy showed structural changes consistent with airway remodeling. Sub-basement membrane thickening was present in every case, but was unrelated to FEV_1 at baseline or after aggressive treatment, or to lability of lung function. Just 1 patient had strong histologic evidence of airway inflammation. All of the children had significant improvement in lung function during evaluation, despite the presence of airway structural alterations. Mean FEV_1 increased from 69.5% to 100.8% of predicted.

In children with severe, persistent asthma, airway remodeling can occur at a young age and despite aggressive glucocorticoid therapy. Most patients in this series show little or no evidence of airway inflammation. Even with significant remodeling, children with severe asthma can achieve near-normal lung function. Although the study is small, the results raise questions about the "inflammatory paradigm" of severe asthma.

COMMENT: *We still understand so little about the pathophysiology of childhood asthma. When does chronic inflammation lead to irreversible airway remodeling, and how do we measure these changes? Endobronchial biopsy of the asthmatic airway may be the only way to begin to answer these critical questions. This study of severe childhood asthmatics reveals significant airway remodeling despite normal lung function and good protective treatment. There is still so much work and research to be done in this area.*
A. L. L.

Jenkins HA, Cool C, Szefler SJ, et al: Histopathology of severe childhood asthma: a case series.
Chest 124:32-41, 2003. ♦♦

High Melatonin Levels Linked to Nocturnal Asthma Exacerbations

PATIENTS with nocturnal asthma have nighttime increases in airway inflammation, in association with decreased lung function and sleep-disrupting symptoms. Melatonin, the main hormone produced by the pineal gland, plays a key role in circadian regulation. This study examined associations between circadian variations in melatonin and the severity of nocturnal asthma.

The observational study included 20 patients with asthma, 7 nocturnal and 13 non-nocturnal; and 11 healthy controls. Measured after 1 week of a regular sleep-wake routine, peak melatonin level was 67.6 pg/mL in the patients with nocturnal asthma, compared with 53.5 pg/mL in controls. Within the nocturnal asthma group, peak serum melatonin level was significantly and inversely correlated with the nighttime change in FEV_1.

Patients with nocturnal asthma have elevated levels of endogenous melatonin. In addition, rising melatonin levels are inversely related to nighttime worsening of FEV_1 in this group of patients. Although further study is needed, the findings may help to explain the benefits of chronotherapeutic corticosteroid dosing on airway inflammation in patients with nocturnal asthma.

COMMENT: *The sleep experts from Denver report that patients with nocturnal asthma had elevations and some delay in peak levels of melatonin in the early morning hours. Melatonin has previously been shown to have proinflammatory properties, particularly for Th2 responses. Although the authors conclude that exogenous melatonin may be deleterious for asthmatics, the implications for chronotherapeutic dosing of corticosteroids may be more germane to allergy practice.*
S. M. F.

Sutherland ER, Ellison MC, Kraft M, Martin RJ: Elevated serum melatonin is associated with the nocturnal worsening of asthma.
J Allergy Clin Immunol 112:513-517, 2003. ♦♦

Enzyme Potentiated Desensitization Is Ineffective, Trial Finds

SOME reports have suggested enzyme potentiated desensitization (EPD) as a simple, low-dose approach to multiple pollen desensitization in patients with seasonal rhinitis. Several small studies have supported the effectiveness of a single preseason injection in reducing hay fever symptoms. A larger, more rigorous trial of preseason EPD is reported.

The U.K. study included 183 adult patients with at least a 2-year history of severe hay fever during the summer months. All had a positive skin-prick response to timothy grass pollen. Patients were randomized to active preseason EPD, two injections given 8 weeks apart; or placebo.

The active EPD and placebo groups had similar clinical outcomes on all measures, including percentage of symptom-free days, quality of life, symptom severity, and change in skin prick or conjunctival provocation threshold. There were no significant adverse reactions in either group.

In hay fever patients with grass-pollen allergy, preseason EPD does not improve clinical outcomes, compared with placebo. The results differ from those of previous trials of EPD; however, aside for possible variations in desensitizing potency, no reason for the lack of treatment effect in this study can be identified.

COMMENT: *In spite of the fact that EPD has been listed as a nonrecommended procedure in practice guidelines, it is still being used, particularly in Europe. Advocates of EPD cite six small studies using weak outcome criteria. This well-designed, reasonably large, double-blind placebo-controlled study should put to rest any belief that EPD can be considered efficacious. Sometimes negative study results can produce positive outcomes in the improvement of care.*
S. M. F.

Radcliffe MJ, Lewith GT, Turner RG, et al: Enzyme potentiated desensitization in treatment of seasonal allergic rhinitis: double-blind randomised controlled study. **BMJ** 327:251-257, 2003. ♦♦

Possible New Therapy for Mast Cell Disease

MUTATIONS of the stem cell factor receptor ckit are thought to play a pathogenetic role in mast cell disease. In vitro studies have identified the tyrosine kinase inhibitor imatinib as a potent inhibitor of ckit, both wild-type and mutant. The clinical effects of imatinib treatment in patients with mast cell disease were evaluated.

The prospective study included 12 adult patients with mast cell disease, confirmed by bone marrow biopsy. All were treated with imatinib, 100 or 400 mg/d. The patients were followed up for mast cell cytoreduction in bone marrow biopsies and for clearance of mast cell skin lesions.

Of 10 evaluable patients, 5 had a measurable response to imatinib therapy. Of 5 patients with eosinophilia, 3 had dramatic clinical responses, going into complete clinical and histologic remission within 12 weeks. All 3 of these patients were negative for the common D816V ckit mutation; the other 2 were D816V positive and had no response to imatinib.

All other patients were D816V negative and free of eosinophilia. Two patients with aggressive, treatment-refractory systemic mastocytosis had a significant reduction in bone pain along with mast cell cytoreduction in bone marrow.

Imatinib shows clinical activity in patients with systemic mast cell disease. This treatment may inhibit the growth-promoting role of wild-type ckit, or may act against some unknown oncogenic kinase. Patients with eosinophilic mast cell disease may have a particularly good response to imatinib.

COMMENT: *Activating mutations in ckit, the receptor for stem cell factor, have been implicated in the pathogenesis of mast cell disease. Despite data showing that imatinib is a potent inhibitor of wild-type and specific mutant ckit, there have been no reports of using this drug to treat mast cell disease. This Mayo Clinic study prospectively treated 12 patients with proven mast cell disease. Of 10 patients who could be assessed for response, 5 had significant mast cell reduction, with 2 in complete remission. Of 5 patients with eosinophilia, 3 had complete remission and 2 were nonresponders. The latter were the only patients with the ckit D816V mutation. This small but exciting study opens up a new door to the treatment of a devastating disease.*
E. J. B.

Pardanani A, Elliott M, Reeder R, et al: Imatinib for systemic mast-cell disease.
Lancet 362:535-537, 2003. ♦♦

Churg-Strauss Syndrome: Roles of ANCA and LTRAs

THREE classifications of Churg-Strauss syndrome have been published. Lanham's criteria emphasize clinical features, while the American College of Rheumatology and Chapel Hill consensus conference criteria focus on pathologic findings. Perinuclear antineutrophilic cytoplasmic antibodies (ANCA) are a common finding in patients with this syndrome; it is unclear whether leukotriene receptor antagonists (LTRAs) play a causative or unmasking role. These two factors were correlated with disease activity in a large series of patients with Churg-Strauss syndrome.

A review of records from 1990 to 2000 identified 91 patients meeting any of the three sets of criteria. The patients were 51 males and 40 females, mean age 49 years. Fifty-two patients met all three sets of criteria, but none of the classification schemes identified all patients.

The clinical manifestations were similar to those described in previous studies--83% of patients had asthma before developing vasculitic symptoms. In 74 patients undergoing ANCA testing, positivity rates were 73% for those tested before treated and 75% for those tested during a disease flare, compared with 16% for those tested during remission. The only clinical finding significantly correlated with ANCA status was CNS involvement.

Of 23 patients receiving LTRAs, 70% started treatment before diagnosis and 27% during remission. Treatment with LTRAs had no significant impact on time from asthma onset to vasculitic symptoms or on organ systems involved. The exception was paranasal sinus involvement, which was present in nearly all treated patients.

None of the current classification schemes identifies all patients with Churg-Strauss syndrome, but the combination of the three systems identifies over 90% of cases. The results suggest that ANCA levels are correlated with disease activity, but do not support any pathogenetic role of LTRAs.

COMMENT: *This large study from the Mayo Clinic Rochester answers some important ongoing questions related to Churg-Strauss syndrome. Of three proposed classification schemes for this condition, none can be used in isolation to identify all patients with active disease. The frequency of ANCA in active disease justifies its inclusion in the diagnostic criteria. As well, the myeloperoxidase-ANCA levels correlate with disease activity. Most importantly, the time between onset of asthma and vasculitis was not affected by LTRA use.*
E. J. B.

Keogh KA, Specks U: Churg-Strauss syndrome: clinical presentation, antineutrophil cytoplasmic antibodies, and leukotriene receptor antagonists.
Am J Med 115:284-290, 2003. ♦♦

More on the Hygiene Theory

A growing body of evidence suggests that childhood exposure to pets or farm animals during childhood actually reduces the risk of allergic disease. On balance, however, current data provide no clear guidance on this issue. The relationship between childhood pets and adult allergic disease was assessed in a European population-based study.

The study included interview data from 18,530 ➤➤

subjects participating in the European Community Respiratory Health Survey. For most subjects, specific IgE to common aeroallergens was measured as well. Atopic adults who kept cats in childhood were more likely to have asthma. This relationship was stronger in areas where cats were less common, with odds ratios (ORs) for wheezing ranging from 1.84 for areas where less than 40% of respondents reported cat ownership to 0.98 (nonsignificant) in areas with a 60% or greater prevalence of cats.

Owning a dog increased the risk of asthma among nonatopic subjects, with ORs of 1.28 for childhood dog exposure and 1.31 for adulthood dog exposure. However, for atopic subjects, childhood dog exposure was associated with a lower risk of hay fever, OR 0.85; and no increase in asthma risk. Keeping birds in childhood was associated with an increased rate of adult respiratory symptoms, OR 1.12.

The effects of childhood pet exposure on adult allergic diseases depend on the type of pet, atopic status, and the extent of pet allergen in the local community. Where the community prevalence of cats is low, growing up with a cat appears to increase the rate of asthma in atopic adults. The results also suggest that dogs may have an "antiallergic but proinflammatory" effect while birds have a "nonspecific proinflammatory" effect.

COMMENT: *These researchers attempt to answer that eternal question: Are animals good or bad for allergic patients? The 18,530 patients were given questionnaires to provide childhood information retrospectively. The effect of pet ownership in childhood varied according to the type of pet and the presence of animals, particularly cats, in the community. Children with cats were more likely to become sensitized allergic adults if they lived in communities with a low cat prevalence. However, there was no increased risk of asthma if there was a cat in the home when cats were prevalent in a community. Although this study does not give our patients definitive answers, it seems to support the hygiene hypothesis.*
S. M. F.
Svanes C, Heinrich J, Jarvis D, et al: Pet-keeping in childhood and adult asthma and hay fever: European Community Respiratory Health Survey.
J Allergy Clin Immunol 112:289-300, 2003. ♦♦

HYGIENE and lifestyle factors have led to major changes in the intestinal microflora of the newborn; antibiotics could play a role as well. Another possible factor is cesarean delivery, which may result in delayed colonization of the intestine after birth. This study assessed the impact of cesarean delivery and antibiotic use on the later development of food allergy in infants and young children.

The Norwegian Birth Registry was used to assemble data on mode of delivery, use of antibiotics by the mother and newborn, and other factors on a cohort of 2,803 babies born in Oslo. The infants were followed up through age 2, when parental reports of allergy to egg, fish, or nuts were assessed.

For children of atopic mothers, cesarean delivery was associated with a 7-fold increase in the risk of parentally reported food allergies. The association between mode of delivery and food allergy was much weaker in children of nonatopic mothers. Antibiotic use did not appear to affect the risk of allergy.

For children of allergic mothers, cesarean delivery is associated with an increased risk of food allergy by age 2. The lack of colonization of the child's intestine by the mother's bacteria might account for this relationship. With further study, this link might weigh on decisions regarding mode of delivery.

COMMENT: *There is abundant speculation about the roles of bacteria (or bacterial products such as endotoxin) in the development of an infant's immune competencies and biases, including allergies. Colonization of a newborn's intestine, occurring naturally at birth in vaginal deliveries, may be the key element in this process. This study shows that infants born to atopic mothers by cesarean section had a 4- to 7-fold greater incidence of food allergies than children delivered vaginally. Enterobacterial colonization differences in infancy may be the explanation.*
R. J. M.
Eggesbo M, Botten G, Stigum H, et al: Is delivery by cesarean section a risk factor for food allergy?
J Allergy Clin Immunol 112:420-426, 2003. ♦♦

Step Up or Step Down?

CURRENT guidelines call for "stepping down" the dose of inhaled corticosteroids once good asthma control has been achieved. However, there are few data on the effectiveness of this approach over the long term or in patients with moderate to severe asthma. This study examined the effects of the step-down approach on disease control in patients with chronic stable asthma

The study included 259 adult patients from Scottish general practices receiving regular, high-dose inhaled corticosteroids for asthma. Mean dose was 1,430 µg. Patients were randomized to the step-down approach, with a 50% reduction in the inhaled corticosteroid dose; or to a control group, with no change in dosage. Asthma exacerbation rates and other outcomes were compared between groups.

In the step-down group, corticosteroid dosage was reduced by an average of 348 µg, or 25% less than in the control group. The dose reduction was achieved with no significant difference in asthma exacerbation rate: 31% for the step-down group vs 26% for controls. Other outcomes were similar as well, including office or hospital visits and general and disease-specific health status.

For patients with chronic stable asthma taking high-dose inhaled corticosteroids, the daily medication dose can be safely reduced without adversely affecting disease control. The randomized, primary care trial includes the types of patients seen in general medical practice, including smokers; and emphasizes practical clinical outcomes.

COMMENT: *Step-down therapy has been recommended by most asthma experts and by most asthma treatment guidelines, without good supportive evidence. In this study of Scottish general practices, there were no differences in asthma outcomes for patients who* ➤➤

reduced their corticosteroid dosage by 25%. We can't say "less is better," but it may be "as good as more."
A.M.
Hawkins G, McMahon AD, Twaddle S, et al: Stepping down inhaled corticosteroids in asthma: randomized controlled trial.
BMJ 326:1115-1118, 2003. ♦♦

Study Looks at Viral Triggers of Acute Asthma and COPD

RECENT studies have highlighted the importance of viral infections as triggers of acute exacerbations of asthma and chronic obstructive pulmonary disease (COPD). A polymerase chain reaction-based test for common respiratory viruses was used to examine the viruses involved in near-fatal asthma and acute exacerbations of asthma or COPD.

Lower respiratory tract secretions were sampled from three groups of hospitalized patients; 17 with near-fatal asthma, 35 with acute asthma, and 14 with COPD. The PCR-based method was designed to detect six respiratory viruses linked to asthma exacerbations: picornavirus, respiratory syncytial virus, parainfluenza virus, influenza A and B viruses, and the adenoviruses. Sputum specimens were obtained during the quiescent phase from 29 patients who were virus-positive during the acute phase.

The positivity rate for viral nucleic acids was 52% in acute-phase specimens, compared with 7% in quiescent-phase specimens. In the acute phase, proportions of virus-positive patients were similar for the three diagnostic groups. Picornavirus was the most frequent virus in the near-fatal asthma group, 47%; followed by adenovirus, 24%. Influenza virus was identified in 36% of COPD patients. Symptoms associated with positive viral status were runny nose, sore throat, fever, chills, and malaise.

Hospitalized patients with these three respiratory diagnoses have a high rate of infection with common respiratory viruses. Acute asthma exacerbations are commonly associated with picornavirus and adenoviruses, while COPD is associated with influenza viruses. Prevention and treatment of respiratory viral infections might be an important therapeutic goal in patients with asthma and COPD.

COMMENT: *This prospective study assessed the association between six common respiratory viruses with hospitalizations for near-fatal asthma, acute asthma, and COPD. Picornavirus and adenovirus were most commonly identified in near-fatal asthma, whereas influenza virus was predominant in COPD. These observations may be useful in developing therapeutic interventions for these conditions.*
E. J. B.
Tan WC, Xiang X, Qiu D, et al: Epidemiology of respiratory viruses in patients hospitalized with near-fatal asthma, acute exacerbations of asthma, or chronic obstructive pulmonary disease.
Am J Med 115:272-277, 2003.

Classification Predicts Asthma Morbidity During Pregnancy

THE 1993 classification of asthma during pregnancy included mild, moderate, and severe categories, based on symptoms and pulmonary function. However, the association between these categories and asthma morbidity during pregnancy has not been assessed. The effects of asthma severity on risk of asthma exacerbations during pregnancy were evaluated.

Of 2,562 pregnant women with asthma identified from 1994 to 2000, complete data were available in 1,739. Based on symptoms, pulmonary function, and medication needs, asthma was classified as mild in 50.2% of women, moderate in 46.8%, and severe in 3.0%. Most of the women were African-American, unmarried, and receiving government assistance.

Initial asthma severity was significantly associated with various morbidity outcomes, including hospitalizations, unscheduled medical visits, corticosteroid dosage, and asthma symptoms during labor and delivery. The asthma exacerbation rate was 12.6% for patients initially classified as having mild disease, compared to 25.7% in the moderate group and 51.9% in the severe group. The increased morbidity in the moderate and severe groups was similar, whether the classification was based on symptoms, spirometry, or medication needs.

During pregnancy, 30.3% of women initially in the mild group were reclassified as having moderate or severe asthma, while 22.9% of those in the moderate or severe group were reclassified as mild. When severity classification changed, so did the associated morbidity.

The asthma classification evaluated in this study corresponds well to the risk of asthma exacerbations and morbidity during pregnancy. Daily medication requirement is an important factor to consider in classifying asthma severity in pregnant women. For many women, asthma severity increases or decreases during pregnancy.

COMMENT: *Although this study of pregnant asthmatics is based on a 10-year-old classification system, the findings are still relevant. Exacerbations occurred in only 12.6% of patients classified as having "mild asthma," which would probably correlate with the current NHBLI "mild-intermittent asthma" classification. Those classified as "moderate" by the old system would probably fall into either the "mild-persistent" or "moderate-persistent" categories. Although the exacerbation rate for these patients is double that for the "mild" category, there may be no substantial advantage in differentiating the mild-persistent from the moderate-persistent patients, since there was considerable switching between categories during the course of pregnancy. Most of the patients were single mothers from lower socioeconomic areas, which may also influence the study findings.*
S. M. F.
Schatz M, Dombrowski MP, Wise R, et al: Asthma morbidity during pregnancy can be predicted by severity classification.
J Allergy Clin Immunol 112:283-288, 2003. ♦♦

Other Diagnoses Are Common in Patients with "Difficult" Asthma

FIVE to ten percent of asthma patients have continued symptoms despite treatment. A series of patients with such "difficult-to-treat" asthma were evaluated to identify other possible contributing factors.

The investigators identified 100 patients with difficult asthma, based on the presence of continued symptoms despite high-dose inhaled corticosteroids, over 1,000 µg/d beclomethasone dipropionate, and long-term treatment with a long-acting β_2-agonist or theophylline. Evaluation in a tertiary respiratory unit identified diagnoses other than asthma in 12 patients, including chronic obstructive pulmonary disease in 6. Another 7 patients had additional diagnoses, most commonly bronchiectasis.

In 55 of the remaining patients, the diagnosis of asthma was confirmed by the finding of reversible airflow narrowing or peak flow variability. However, both of these findings were absent in another 20 patients. Among the patients with confirmed asthma, nonadherence to prescribed prednisolone therapy was a frequent finding. In 10 patients, psychiatric factors appeared to be a major contributor to respiratory symptoms. Several patients continued to keep pets despite sensitization, while others had a history of aspirin sensitivity.

This descriptive study identifies a wide range of contributing factors in patients with "difficult-to-treat" asthma. Systematic assessment identifies other diagnoses instead of or in addition to asthma in nearly one-third of such patients. Treatment noncompliance and psychiatric factors are common as well.

COMMENT: *This is an excellent descriptive study looking at reasons to explain "difficult-to-treat" asthma. In this setting, the diagnosis was reconfirmed (12% were misdiagnosed) and comorbidities were established (7% were previously unrecognized). Other findings included irreversible airway changes in 20% of patients, a psychiatric component in 10%, and frequent medication noncompliance, including not using prescribed prednisolone in 9 of 18 patients. This study demonstrates the continuing need to reassess the asthma patient, particularly one who is difficult to treat.*
G. D. M.
Robinson DS, Campbell DA, Durham SR, et al: Systematic assessment of difficult-to-treat asthma.
Eur Respir J 22:478-483, 2003. ♦♦

More on Anti-IgE

ADDING the anti-IgE agent omalizumab to standard asthma therapy reduces the exacerbation rate while decreasing the need for inhaled corticosteroids and rescue medications. An extension phase was added to a randomized trial to evaluate the long-term effectiveness of omalizumab in patients with severe allergic asthma.

In the original trial, 525 patients were randomized to receive subcutaneous injections with placebo or omalizumab, minimum dose 0.016 mg/kg/IgE, every 4 weeks for 16 weeks, while continuing their previous inhaled corticosteroid therapy. Over the subsequent 12 weeks, controlled attempts were made to reduce their inhaled corticosteroid dose. In the 24-week extension phase, patients continued on their assigned placebo or omalizumab therapy and on the lowest sustainable dose of inhaled corticosteroid.

For the 460 patients enrolled in the extension phase, omalizumab was associated with a significantly reduced exacerbation rate: 0.60 exacerbations per patient, compared with 0.83 in the placebo group. This was despite the lower inhaled corticosteroid dose in the omalizumab group: mean beclomethasone dipropionate equivalent dose was 227 vs 335 µg/d. Both groups had a low rate of adverse events.

Anti-IgE therapy with omalizumab appears effective for long-term disease control in patients with severe allergic asthma. Omalizumab is safe and well-tolerated, providing a reduced risk of exacerbations at a lower inhaled corticosteroid dose. Omalizumab may also lead to improved lung function.

COMMENT: *In this follow-up study and accompanying thoughtful editorial, the long-term efficacy and safety of anti-IgE are noted. This is another important piece of an evolving picture. Longer follow-up will be necessary to establish the true value of this innovative but costly approach to severe asthma.*
A. M.
Lanier BQ, Corren J, Lumry W, et al: Omalizumab is effective in the long-term control of severe allergic asthma.
Ann Allergy Asthma Immunol 91:154-159, 2003.

ANTI-IgE therapy with omalizumab has been reported beneficial in patients with seasonal allergic rhinitis, including improvements in nasal symptoms and quality of life. A trial of omalizumab for perennial allergic rhinitis (PAR) is reported.

The multicenter study included 289 patients, aged 12 to 70 years, with moderate to severe PAR. All patients had symptoms lasting over 2 h/d for more than 9 months out of the year and were skin-prick positive to dust mite, dog, or cat allergen. They were randomized to receive 16 weeks of treatment with subcutaneous omalizumab, at least 0.016 mg/kg/IgE every 4 weeks; or placebo.

Assessed every 4 weeks, average daily nasal severity score was consistently lower with omalizumab than with placebo. Symptoms of PAR were considered "controlled" in 28% of the omalizumab group vs 10% of the placebo group. The symptom relief provided by omalizumab was even greater among patients who had failed to respond to immunotherapy. The omalizumab group also had a greater reduction in rescue medication use and a higher rating of overall treatment efficacy. Both treatments had a low rate of adverse events.

Omalizumab is a safe and effective treatment for moderate to severe PAR. This form of anti-IgE therapy reduces symptoms and improves disease-related quality of life while reducing the need for rescue antihistamines. Omalizumab may be especially valuable for patients who do not respond to conventional stepwise treatment for PAR. ➤➤

COMMENT: *This report represents an important step in the evolution of anti-IgE therapy. While omalizumab appears to be a safe and effective therapy for PAR, further studies will be needed to compare its effect with conventional, lower-cost modalities.*
A. M.
Chervinsky P, Casale T, Townley R, et al: Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis.
Ann Allergy Asthma Immunol 91:160-167, 2003. ♦♦

Snoring in Preschool Children: Links to Nocturnal Cough and Asthma

MANY asthma patients also have sleep-disordered breathing. A case report described nocturnal cough associated with sleep apnea in a young child, but there are few data on the relationships among snoring, nocturnal cough, and asthma in children. The prevalence of snoring and its association with nocturnal cough and allergic symptoms were examined in a population of preschool children.

The study included a random sample of 974 Australian children, aged 2 to 5 years. In response to a questionnaire, parents reported a 10.5% prevalence of snoring, with no difference between boys and girls. Nocturnal cough was reported for 36.6% of boys and 30.6% of girls. These two symptoms were significantly associated with each other: odds ratio 3.68 (95% confidence interval 2.41 to 5.63). Children who snored were only slightly more likely to be obese.

Asthma was reported for 42.2% of children whom snored, compared with 26.4% of nonsnorers: odds ratio 2.03 (95% confidence interval 1.34 to 3.10). Snoring was associated with an increased prevalence of asthma only among children without hay fever, 41.2% vs 24.8%; not among those with hay fever, 47.1% vs 38.2%.

Snoring is common among preschool children and is significantly related to nocturnal cough and asthma. These respiratory symptoms may share a common cause, so treatment for one symptom may also help to relieve the others.

COMMENT: *Snoring has not been well studied in the pediatric population. A strong association has been made between snoring in adults and obstructive sleep apnea. In this study, children 2 to 5 years of age are shown to have a "snoring" prevalence of 10.5% by questionnaire. These authors also define a strong association between snoring, nocturnal cough, allergic rhinitis, and asthma. Many young children may be ubable to perform pulmonary function tests; snoring may be another clue to establishing the diagnosis of asthma in this age group.*
A. L. L.
Lu LR, Peat JK, Sullivan CE: Snoring in preschool children: prevalence and association with nocturnal cough and asthma. **Chest** 124:587-593, 2003. ♦♦

Eosinophil Measures Don't Predict BHR in Adolescent Asthma Patients in Remission

CHILDREN with asthma often go into clinical remission in adolescence, but many of these patients continue to have bronchial hyperresponsiveness (BHR). It remains unclear whether this persistent BHR results from airway inflammation or some other mechanism. Adolescent asthma patients in clinical remission were studied to see whether BHR is related to peripheral blood eosinophilia and/or serum eosinophil cationic protein (ECP).

The study included 51 adolescents in long-term clinical remission of asthma, with no symptoms or medications during the previous 2 years. Twenty-eight were classified as BHR-positive, based on a methacholine PC_{20} of less than 18 mg/mL; and 23 as BHR-negative. Peripheral blood eosinophil count and serum ECP were compared between groups, as well as in 28 patients with symptomatic asthma and 28 healthy adolescent controls.

Peripheral blood eosinophil count was 262.1/μL in the BHR-positive group and 253.9/μL in the BHR-negative group. There was also no significant difference in serum ECP: 15.6 and 15.8 μg/L, respectively. For BHR-positive patients in remission, both blood measures were similar to those of the healthy control group and different from those of the symptomatic asthma group.

For adolescent patients in long-term asthma remission, peripheral blood eosinophilia and serum ECP level cannot distinguish between those who are BHR-positive and BHR-negative. The mechanism of persistent BHR in patients in remission appears to differ from that of patients with continued asthma symptoms.

COMMENT: *Asthma is variable, particularly in children and adolescents, and patients tend to stop their medications when they feel better. These factors have stimulated the search for a quantitative marker or test to monitor the inflammation in asthma. Unfortunately, we are still searching for the "asthma sed rate." Care for the patient with asthma remains an art based on science.*
D. K. L.
Koh YK, Kang H, Nah KM, Kim CK: Absence of association of peripheral blood eosinophilia or increased eosinophil cationic protein with bronchial hyperresponsiveness during asthma remission.
Ann Allergy Asthma Immunol 91:297-302, 2003. ♦♦

Airborne Allergen Levels: High for Pets, But Low for Mite

MANY questions remain about the link between sensitization to allergens found in the home and the development of asthma. Measurement of airborne allergens has theoretic advantages over measuring allergen levels in dust samples. An ion-charging device was used to measure levels of airborne pet and dust mite allergen.

The study employed the Ionic Breeze Quadra device, which uses an ion-charging technique to sample ➤➤

large quantities of air silently. Air sampling was performed over 24 hours at a rate of 1.7 m^3/min. The airborne particles collected were studied by enzyme-linked immunosorbent assay to measure levels of Fel D 1, Can f 1, Der p 1, and Der f 1. Allergen levels were compared for 32 homes with cats and/or dogs and 12 without pets.

All homes with cats had airborne cat allergen; at normal breathing rates, the amount of Fel d 1 inhaled was calculated at 0.01 to 0.30 µg/d. Even in homes without cats, the range was 0.01 to 0.05 µg/d. Airborne cat allergen levels were significantly correlated with the levels in floor dust samples. A similar pattern was noted for dog allergen, although most homes without dogs did not have Can f 1.

Airborne levels of dust mite allergen were very low, suggesting an inhaled allergen rate of 1 ng/d or less. Mite allergen became detectable when household dust was disturbed.

The use of an ion-charging device measures high levels of airborne pet allergen, especially cat, in homes with and without animals. Where pets are present, exposure to airborne cat or dog allergen may be 100 times higher than exposure to airborne mite allergen. High exposure to animal allergens may lead to the development of immunologic tolerance.

COMMENT: *These authors used an ion-charging technique to sample the air in homes with and without dogs and cats for extended periods. In homes with cats, the level of cat allergen was an order of magnitude higher than the level of dust mite allergen. The authors argue that this difference in exposure helps explain why sensitization to cat and mite occurs with different dose-response patterns (ie, mite exposure is never high enough to result in tolerance). The fact that ambient dust mite allergen levels were very low also helps explain why air filtration in homes has little or no effect on symptoms caused by dust mite allergy.*
S. A. T.

Custis NJ, Woodfolk JA, Vaughn JW, Platts-Mills TAE: Quantitative measurement of airborne allergens from dust mites, dogs, and cats using an ion-charging device. **Clin Exp Allergy** 33:986-991, 2003. ♦♦

Severe RSV in Infants Linked to Later Respiratory Morbidity

PREVIOUS studies have found increased rates of wheezing among infants hospitalized for respiratory syncytial virus (RSV) infection. The rate of such infections is particularly high among children of Alaska Native ethnicity. A group of Alaska Native children with RSV infection were followed up to assess their subsequent risk of respiratory disease.

The researchers identified 204 Alaska Native children hospitalized for RSV between 1993 and 1996, along with 338 controls without hospitalization for lower respiratory infections. All children were less than 2 years old at enrollment. Follow-up data through age 5 to 8 years were available on 95 cases hospitalized with RSV and 113 controls.

Children with a history of RSV hospitalization had significantly higher rates of wheezing, lower respiratory infections, and asthma diagnosis through the first 4 years of life. These associations gradually weakened over time, and were no longer significant by the time the children were 5 years old. At last follow-up, children in the case group were more likely to have an FEV_1/forced vital capacity of less than 85%, relative risk 1.64. Cases also had higher rates of productive cough and increased chest diameter, but not of wheezing or crackles. Children with a history of RSV hospitalization were at no increased risk of allergies, eczema, or positive family history of asthma.

Children with RSV infection severe enough to require hospitalization during the first 2 years of life remain at elevated risk of wheezing, lower respiratory infections, and asthma through age 4. Other risks, including productive cough, may remain elevated through at least age 8. Efforts to prevent RSV infection in infants may prevent respiratory disease later in childhood.

COMMENT: *Longitudinal studies of Alaska Native children, who tend to have severe RSV infections requiring hospitalization, give a unique opportunity to evaluate the risk of subsequent wheezing (and other respiratory illnesses). Children who were hospitalized were more likely to wheeze and to be diagnosed as asthmatic, compared to those whose were not hospitalized. This tendency gradually decreased over a 4-year period.*
J. A. A.

Singleton RJ, Redding GJ, Lewis TC, et al: Sequelae of severe respiratory syncytial virus infection in infancy and early childhood among Alaska Native children. **Pediatrics** 112:285-290, 2003. ♦♦

Viral Challenge Leads to Increased LTC_4 Levels

LOCAL inflammatory mediators may play a role in the development of illness and complications caused by respiratory viruses. Leukotriene C_4 (LTC_4) responses to nasal challenge with common respiratory viruses were measured, including their relationship with developing signs and symptoms of upper respiratory infection (URI).

Sixty-six healthy adult volunteers received intranasal inoculation with safety-tested strains of influenza A virus, rhinovirus, or respiratory syncytial virus. Another 9 subjects served as uninfected controls. All inoculated subjects were infected, as confirmed by viral shedding or seroconversion.

Serial nasal lavages documented significant increases in LTC_4 levels for all three infecting viruses. The increases in local LTC_4 levels were significantly related to the development of respiratory illness, peaking on days 1 to 4 and decreasing on days 5 to 8. Symptom scores and nasal secretion weights were not significantly related to LTC_4 levels.

In this experimental model of URI, intranasal challenge with respiratory viruses is followed by increased levels of locally produced LTC_4. The LTC_4 levels increase in the first few days, as signs and symp- ➤➤

toms develop; then decrease as symptoms resolve. More research is needed to clarify the role of leukotrienes as mediators of upper respiratory viral infections.

COMMENT: *The essential mediators linking upper respiratory viral illness to airway symptoms and complications remain elusive. This group has published extensively on the viral nasal challenge. Increased LTC_4 concentrations in nasal lavage suggest that leukotriene antagonists may be useful in the treatment of URIs or postviral complications such as sinusitis, otitis media, cough, and/or asthma. Time will tell. In the meantime, give the flu vaccine and spare the antibiotics.*
D. K. L.
Gentile DA, Fireman P, Skoner DR: Elevations of local leukotriene C_4 levels during viral upper respiratory tract infections.
Ann Allergy Asthma Immunol 91:270-274, 2003.

Effects of Add-on Therapy on Exhaled Nitric Oxide: Salmeterol vs Montelukast

FOR children taking inhaled corticosteroids for asthma, options of add-on therapy include long-acting β_2-agonists and leukotriene receptor antagonists. Exhaled nitric oxide measurements were performed to compare the effects of add-on therapy with salmeterol and montelukast in asthmatic children.

The controlled trial included 22 children with asthma who continued to have exhaled nitric oxide levels over 12 ppb, despite inhaled budesonide, 400 µg/d. All had normal lung function. While continuing budesonide therapy, the children were randomized to receive montelukast, 5 mg/d; salmeterol, 50 µg; or placebo in double-blind, double-dummy fashion. In crossover fashion, the children received all three treatments for 2 weeks each. Exhaled nitric oxide levels were compared at the end of each treatment.

The geometric mean exhaled nitric oxide level was 20 ppb after treatment with salmeterol, compared to 15 ppb after both montelukast and placebo. There was also a significant 2.63 L increase in FEV_1 after salmeterol, significantly greater than with placebo or montelukast.

In asthmatic children, add-on therapy with salmeterol results in significantly higher exhaled nitric oxide levels than either montelukast or placebo. However, salmeterol achieves greater improvements in bronchodilation in this situation. With montelukast, the reduction in exhaled nitric oxide is no greater than with placebo.

COMMENT: *Debate continues as to the optimal next choice after the use of low-dose inhaled corticosteroid for asthma. Should we monitor symptoms, FEV_1, peak flow, exacerbations, small airway function, or some marker of airway inflammation? Exhaled nitric oxide has been one of the latter but has not performed ideally. The surprise in this study was that an oral leukotriene antagonist did not decrease the exhaled nitric oxide concentration, while salmeterol resulted in an increase in nitric oxide. What does all of this mean? I think we need another study.*
D. K. L.
Buchvald F, Bisgaard H: Comparisons of the complementary effect on exhaled nitric oxide of salmeterol vs montelukast in asthmatic children taking regular inhaled budesonide.
Ann Allergy Asthma Immunol 91:309-313, 2003. ♦♦

REVIEWS OF NOTE

COMMENT: *There has been an ever-increasing interest in the association between rhinitis and asthma. This review covers the epidemiologic evidence demonstrating the coexistence of asthma and rhinitis in the same patient. Emphasis on continuum of disease and opportunities to intervene therapeutically in the interruption of the "allergic march" are discussed.*
E. J. B.
Bousquet J, Vignola AM, Demoly P: Links between rhinitis and asthma. **Allergy** 58:691-706, 2003.

COMMENT: *This detailed review nicely summarizes the world of tree nut allergens from a biochemical and immunologic perspective. The authors are careful to point out the limitations of simply comparing sequence homologies of various tree nuts.*
S. A. T.
Roux KH, Teuber SS, Sathe SK: Tree nut allergens.
Int Arch Allergy Immunol 131:234-244, 2003.

COMMENT: *A comprehensive overview of gastroesophageal reflux; its effects on the respiratory tract, the larynx and pharynx, and sleep; and innovative diagnostic and treatment approaches.*
E. J. B.
Fourth Multi-Disciplinary International Symposium on Supraesophageal Complications of Reflux Disease.
Am J Med 115 (supple 3A):1S-218S, 2003.

COMMENT: *This review succinctly organizes the morass of literature examining the effects of inhaled corticosteroids in our asthmatic patients. Well organized by the various physiologic effects, this report will help all practitioners understand the potential deleterious effects of inhaled corticosteroids.*
S. M. F.
Kelly HW: Potential adverse effects of the inhaled corticosteroids.
J Allergy Clin Immunol 112:469-478, 2003.

COMMENT: *We have read and reread papers on the actions of corticosteroids and listened to countless lectures on the same topic. So why, you ask, should one read yet another review? This information needs repetition for retention. This excellent review provides an overview of the inflammation of asthma and relates it to the actions of corticosteroids. The authors also discuss the multiple molecular mechanisms of corticosteroids, particularly the paradox that corticosteroids reduce proinflammatory mediators yet most of our understanding is that corticosteroids stimulate, not repress, gene transcription. The review is well illustrated* ➤➤

and has a very helpful glossary.
D. K. L.
Barnes PJ, Adcock IM: How do corticosteroids work in asthma? **Ann Intern Med** 139:359-370, 2003. ♦♦

COMMENT: *Immunotherapy for plant pollen allergy can be confusing because of the multitude of species to which humans can be allergic. However, as Dr. Weber elegantly explains, understanding cross-reactivity within taxons can help design rational immunotherapy regimens. This is must reading for all allergists.*
R. J. M.
Weber RW: Patterns of pollen cross-allergenicity.
J Allergy Clin Immunol 112:229-239, 2003. ♦♦

COMMENT: *Does "atopy" mean the same thing as "allergy?" Not necessarily. I still have my notes from a lecture by Hal Nelson some 25 years ago in which he emphasized that the two are not synonymous. Asthma, rhinitis, and eczema are all atopic diseases but need not be allergic or IgE-mediated. This article underscores that point and alludes to treatment differences implied by the distinction.*
R. J. M.
Novak N, Bieber T: Allergic and nonallergic forms of atopic diseases.
J Allergy Clin Immunol 112:252-262, 2003. ♦♦

COMMENT: *This is a very useful review of a topic that allergists confront on a daily basis. Food and drink can make you sick.*
A. M.
Jansen SC, van Dusseldorp M, Bottema KC, Dubois AEJ: Intolerance to dietary biogenic amines: a review.
Ann Allergy Asthma Immunol 91:233-241, 2003. ♦♦

COMMENT: *This article by Dr. Rachelefsky thoroughly reviews the indication for systemic corticosteroids in childhood asthma. Several excellent tables and algorithms are included and are superb references for acute care of the child with an asthma exacerbation. Many important issues are reviewed, including viral induced wheezing, monitoring of asthma, and safety and efficacy issues. The NIH asthma guidelines are referenced throughout the article. Our care of asthmatic children has improved; however, there are still many challenges.*
A. L. L.
Rachelefsky G: Treating exacerbations of asthma in children: the role of systemic corticosteroids.
Pediatrics 112:382-397, 2003. ♦♦

COMMENT: *One of the things that members of the Section on Allergy and Immunology of the American Academy of Pediatrics can take pride in is the annual publication of the "synopsis book." This year, 89 articles from 38 journals are featured, under the direction of Editor Robert A. Wood. The result is great and easy reading!*
J. A. A.
Wood RA, ed: Synopsis book: best articles relevant to pediatric allergy and immunology.
Pediatrics 112 (suppl):453-494, 2003. ♦♦

COMMENT: *This is a practical, "must know" review for the practicing allergist/immunologist. The authors, who have personal experience in this area, summarize the literature and documented diseases related to mold, particularly indoor mold. Suggestions for evaluation are included. This article should be on the clinic bookshelf for ready reference when we see patients with symptoms attributed to mold.*
D. K. L.
Chapman JA, Terr AI, Jacobs RL, et al: Toxic mold: phantom risk vs science.
Ann Allergy Asthma Immunol 91:222-232, 2003. ♦♦

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