AllergyWatch®

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

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Routine Plus As-Needed ICS/LABA Performs Well

CURRENT asthma-treatment guidelines call for early inhaled corticosteroid (ICS) therapy with the addition of a long-acting β_2-agonist if needed for disease control. The ICS budesonide and the LABA formoterol have been used in combination for reliever plus maintenance therapy. The efficacy and costs of this approach were tested in patients with persistent asthma.

The randomized, open-label trial included 1,583 patients, aged 12 years or older. All had persistent asthma despite daily treatment with ICS, alone or with LABA. Patients in the intervention group received maintenance and reliever therapy with budesonide/formoterol, 160/4.5 µg twice daily and as needed. Controls were treated according to conventional best practice; in both groups, treatment continued for 6 months. The main outcomes of interest were severe asthma exacerbations, use of reliever medications, and total ICS dose. Costs were assessed as well.

The two groups were similar in time to first severe exacerbation and rate of severe exacerbations. There was a 41% reduction in the number of emergency room or hospital visits among patients receiving budesonide/formoterol maintenance and reliever therapy, although the difference was not significant. The intervention group had a 26% reduction in mean ICS dose and a 14% reduction in use of reliever medications. Budesonide/formoterol maintenance and reliever therapy was also associated with lower costs, including costs for asthma medications and total costs per patient. In a subset of 115 patients, sputum eosinophil counts were similar and well-controlled in both groups.

For patients with persistent asthma, budesonide/formoterol maintenance and reliever therapy controls disease at least as well as current guideline-based therapy. The ICS/LABA maintenance/reliever combination lowers ICS dose and costs while maintaining good control of airway inflammation.

COMMENT: *This study compares fixed and reliever therapy with budesonide and formoterol to conven-*➤➤

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

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

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tional management. Similar or improved clinical control was achieved compared to conventional practice. Of note, cost and costicosteroid dose were lower while control of eosinophilic inflammation was maintained.
B. E. C.
Sears MR, Boulet L-P, Laviolette M, et al: Budesonide/formoterol maintenance and reliever therapy: impact on airway inflammation in asthma.
Eur Respir J. 2008;31:982-989. ♦♦

NEJM Addresses SLIT

INJECTION immunotherapy is the routine treatment for allergy symptoms in the United States, and is the only form of immunotherapy currently approved by the Food and Drug Administration. In Europe, sublingual immunotherapy (SLIT) was introduced as an alternative to subcutaneous immunotherapy, despite the lack of efficacy data at that time. After presenting a case vignette of a patient with hay fever, this article discusses the evidence on SLIT as a treatment option.

In Europe, SLIT is now commonly used for patients who might otherwise receive injection immunotherapy. The only commercially available SLIT product is Grazax, a grass-pollen extract--in the United States, no agent has yet been approved for SLIT. Patients can start SLIT at the full maintenance dose, without the gradual dose increase used in injection immunotherapy. Trials and clinical experience support the efficacy of SLIT, although most patients continue to take other medications for symptom relief. Clinically, a variety of SLIT approaches are being used in the absence of sound clinical trial data, including untested allergens and combination allergen preparations. The cost of SLIT is approximately $1,700 per year.

Local irritation is the main side effect of SLIT; no cases of anaphylaxis have been reported with Grazax. Issues of standardization in allergen immunotherapy pose special problems in SLIT, which uses doses many times higher than would be used in injection immunotherapy. The efficacy of allergen combinations formulated in the allergists' office has not been adequately tested. Questions also remain as to the optimal duration of SLIT, its relative efficacy compared with injection immunotherapy, and its effectiveness in children.

For the patient presented in the case vignette--a busy professional predominantly sensitized to grass pollen--the author would recommend a 3-month trial of SLIT before pollen season. At the end of the season, the patient would be re-evaluated to consider the use of a full 3-year course of therapy. The lack of international consensus regarding the role of SLIT is reflected in the absence of specific protocols in allergy treatment guidelines.

COMMENT: *Sublingual immunotherapy is enjoying some time in the sun, especially in Europe. This clinical vignette provides an opportunity to discuss SLIT, including the lack of an FDA-approved product in this country, the lack of comparison studies between SLIT and subcutaneous immunotherapy, the lack of evidence of an effect of low doses, concerns about the absorptive capacity of the oral mucosa for multiple allergens, the lack of protocols for duration of therapy, the lack of evidence of efficacy in children, and the substantial cost for all this uncertainty (about $1,700 per year in Europe). On what basis are some U.S. doctors already offering this treatment? Is there an ethical issue to be considered?*
R. J. M.
Frew AJ: Sublingual immunotherapy.
N Engl J Med. 2008;358:2259-2264. ♦♦

New Data on Course of Responses to Immunotherapy

ALLERGEN-specific immunotherapy effectively modifies the response to antigen in patients with seasonal allergic rhinitis. The response to immunotherapy involves both cellular and humoral regulatory mechanisms, but the process by which induction and maintenance of allergen-specific immune tolerance evolves has never been studied in detail. This was done in a group of patients undergoing immunotherapy for seasonal allergic rhinitis.

The study included 18 patients with severe seasonal allergic rhinitis caused by grass pollen. The patients were randomized to receive 1 year of immunotherapy with alum-adsorbed grass pollen vaccine or placebo injections. Repeated evaluations of early- and late-phase responses to intradermal allergen and cellular responses to grass pollen allergen were performed. Serum levels of allergen-specific IgG4 and IgA were measured, and inhibitory activity was assessed in biologic assays of IgE responses.

Patients receiving active grass pollen immunotherapy had reductions in symptom scores and conjunctival reactivity. At 2 to 4 weeks after the start of treatment, while allergen doses were low, active immunotherapy was associated with increased production of interleukin-10 (IL-10) and inhibition of late-phase skin responses. Serum allergen-specific IgG4 and IgA appeared at 6 to 12 weeks, at higher allergen doses, together with inhibitory antibody activity for basophil histamine release and IgE-facilitated allergen-binding to B cells. These changes occurred before inhibition of early-phase skin responses.

The results lend new insights into the time course of immunologic and clinical responses to immunotherapy in patients with seasonal allergic rhinitis. Increases in IL-10 production occur before clinical responses. Inhibitory antibodies appear later on, and might be needed for modulation of IgE-mediated events and clinical efficacy.

COMMENT: *The immunologic changes induced by allergen immunotherapy include early induction of IL-10 and concomitant suppression of late cutaneous allergen responses within the first 2 to 4 weeks, even before a significant clinical effect. After 6 to 12 weeks, allergen-specific IgG4 and IgA increase and there is suppression of early allergen skin responses as well as good clinical response. Could the early IL-10 response be used to predict clinical efficacy for sublingual immunotherapy?*
S. M. F.

Francis JN, James LK, Paraskevopoulos G, et al: Grass pollen immunotherapy: IL-10 induction and suppression of late responses precedes IgG4 inhibitory antibody activity.
J Allergy Clin Immunol. 2008;121:1120-1125. ♦♦

Allergy to High-Molecular-Weight Agents May Resolve

EXPOSURE to high-molecular-weight agents can cause allergic symptoms in workers in a wide range of occupations, including bakers (flour) and health care professionals (latex). There are few prospective data on the health risks associated with these occupational exposures. Apprentices in various occupations were studied to assess the long-term occupational allergy outcomes of exposure to high-molecular-weight agents.

The prospective study included subjects exposed to high-molecular-weight allergens during apprenticeship programs in animal health, pastry-making, and dental hygiene. Assessments included a respiratory symptom questionnaire, skin-prick tests, spirometry, and methacholine challenge testing. The analysis focused on the incidence and remission of sensitization, allergic symptoms, and bronchial hyperresponsiveness. Follow-up continued into the years after the end of the apprenticeship program.

The study included 384 subjects, of whom 78% held a job related to their apprenticeship program during follow-up. In this group, the incidence of sensitization was 1.3 per 100 person-years. Other incidences per 100 person-years were 1.7 for rhinoconjunctivitis symptoms, 0.7 for chest symptoms, and 2.0 for bronchial hyperresponsiveness.

Among apprentices who became sensitized during training, the rate of lost sensitization was 18.5 per 100 person-years for those who held jobs unrelated to their training versus 9.5 per 100 person-years for those who remained in the same field. For those no longer in jobs related to their apprenticeship, other remission rates per 100 person-years were 9.6 for rhinoconjunctival and chest symptoms and 12.4 for bronchial hyperresponsivness. Several characteristics associated with the incidence and remission of all outcomes were identified.

For apprentices with occupational exposure to high-molecular-weight agents, rates of sensitization, allergic symptoms, and bronchial hyperresponsiveness are higher during the apprenticeship than during subsequent work years. Among workers who develop symptoms during apprenticeship, remission rates are higher for those who go into jobs unrelated to their training. Similar studies in workers exposed to low-molecular-weight agents are needed.

COMMENT: *This study followed more than 400 workers exposed to high-molecular- weight occupational allergens from apprenticeship through the first 8 years of their careers. The striking finding was that many sensitized workers improve despite continued exposure to the offending allergen. The exact mechanism for this is unclear.*
B. E. C.

Gautrin D, Ghezzo H, Infante-Rivard C, et al: Long-term outcomes in a prospective cohort of apprentices exposed to high-molecular-weight agents.
Am J Respir Crit Care Med. 2008;177:871-879. ♦♦

Early Dog Ownership Reduces Sensitization

THERE are conflicting data as to how dog ownership during childhood affects the later development of allergies. Although most studies have suggested a protective effect of childhood dog ownership and aeroallergen sensitization, others have found no such relationship. This study evaluated the possible role of endotoxin exposure in the relationship between dog exposure and childhood allergic sensitization and atopy.

The study included data from two German birth cohort studies: 1,962 subjects from the German Infant Nutrition Intervention Programme (GINI) and 1,193 from the Influences of Lifestyle Related Factors on the Human Immune System and Development of Allergies in Children (LISA). Both studies included data on contact with dogs and exposure to indoor endotoxin during infancy and early childhood, as well as on allergic symptoms and physician-diagnosed allergic disease up to age 6.

Dog ownership was linked to a significant reduction in the risk of mixed pollen and inhalant allergen sensitization. This protective effect was particularly strong among children exposed to a family dog during the first year of life. In contrast, exposure to dogs outside the home, without dog ownership, was unrelated to sensitization. In addition, dog ownership in early childhood showed no association with sensitization to dog or with allergic symptoms and allergic diseases at follow-up.

Exposure to house dust endotoxin during infancy was unrelated to later sensitization. The protective effects of dog ownership remained significant after stratification for parental history of allergic disease and among children without home exposure to environmental tobacco smoke.

As in most previous reports, this study finds that dog ownership during early childhood is associated with a reduced risk of sensitization to inhalant allergens. This effect is unrelated to indoor endotoxin exposure during infancy. Dog ownership and contact are unrelated to the prevalence of allergic disease and allergic symptoms from age 4 to age 6.

COMMENT: *Dog ownership in early childhood was associated with a low prevalence of pollen and inhalant sensitization over time. Of interest is the finding that exposure to house dust endotoxin did not affect outcomes. The hygiene hypothesis remains an enigma.*
B. E. C.

Chen C-M, Morgenstern V, Bischof W, et al: Dog ownership and contact during childhood and later allergy development.
Eur Respir J. 2008;31:963-973. ♦♦

Five Phenotypes of Early Childhood Cough and Wheeze

IT is important to distinguish among the several distinct disorders that may be classified as childhood asthma. Traditional phenotype definitions have important limitations--they are generally limited to a single dimension of disease and may not reflect the underlying disease process. A technique called latent class analysis, developed to identify distinct subsets within heterogeneous populations, was used to analyze different phenotypes of childhood asthma.

The study included longitudinal data on a population-based cohort of 1,650 preschoolers, including 319 with parent-reported wheezing or chronic cough. Latent class analysis--including multidimensional data on symptoms, skin-prick tests, pulmonary function, and airway responsiveness--was performed to define patient subsets. Follow-up data were used to compare outcomes of children in the different phenotype groups at school age.

Latent class analysis identified three wheezing phenotypes, atopic persistent wheeze, nonatopic persistent wheeze, and transient viral wheeze; and two cough phenotypes, persistent cough and transient cough. On outcome analysis, rates of subsequent wheezing, chronic cough, and use of inhaled medications differed significantly among these five groups. The five phenotypes were similar to traditional definitions in some important ways. At the same time, they helped to resolve discrepancies with previous categorization: eg, transient vs persistent wheeze and viral vs multiple-trigger wheezing.

Using a multidimensional approach, latent class analysis identifies clinically relevant phenotypes of cough and wheezing in preschoolers. These definitions may be of value for research and clinical purposes. Similar studies should be performed in adult obstructive airway diseases, for which definition of phenotypes is just as important.

COMMENT: *This excellent study of over 1,600 children phenotypes both cough and wheeze with a very thorough characterization. Of note is the lack of decrement in lung function among transient wheezers that was found in the Tucson Children's Respiratory Study. This type of analysis will help better define groups for natural history studies.*
B. E. C.

Spycher BD, Silverman M, Brooke AM, et al: Distinguishing phenotypes of childhood wheeze and cough using latent class analysis.
Eur Respir J. 2008;31:974-981. ♦♦

Anti-IL-5 Therapy Is Effective in HES

PATIENTS with hypereosinophilic syndrome (HES) have persistently high blood eosinophil levels with no identifiable cause, leading to end-organ damage and thromboembolic events. Most patients respond to corticosteroids, but side effects and adverse events are common. Mepolizumab, an anti-interluekin-5 (IL-5) monoclonal antibody, was tested for safety and efficacy in HES.

The multinational randomized trial included 85 patients with HES, with blood eosinophil counts of 1,500/mL or higher and eosinophil-related organ involvement and no identifiable secondary cause. All patients were negative for the *FIPL1L1-PDGRA* fusion gene, which represents a myeloproliferative variant ➤➤

of HES. All required prednisone monotherapy, 20 to 60 mg/d, to achieve stable clinical status with an eosinophil count of less than 1,000/mL.

Patients were randomly assigned to treatment with intravenous mepolizumab or placebo, with tapering of the prednisone dose over 32 weeks. The percentage of patients achieving a prednisone dose of 10 mg/d or less for at least 8 weeks was compared between groups.

Eighty-four percent of patients assigned to mepolizumab met the primary endpoint, compared with 43% of the placebo group: hazard ratio (HR) 2.90. Mepolizumab responders showed no increase in disease activity. Blood eosinophil counts dropped to less than 600/mL for 8 or more weeks in 95% of the mepolizumab group compared to 45% of the placebo group, HR 3.53. There were 14 serious events, including one death, in 7 patients assigned to mepolizumab, compared to 7 serious events in 5 patients in the placebo group.

Anti-IL-5 therapy with mepolizumab can lower blood eosinophil count while maintaining disease control in patients with HES. This treatment enables significant reductions in corticosteroid dose, including steroid discontinuation in many patients. An ongoing extension phase will provide data on long-term safety.

COMMENT: *Eosinophils are capable of being the primary effector cells in certain inflammatory diseases, such as HES, a rare multiorgan disease for which systemic steroids are the main treatment. Interleukin-5 is thought to be the principal cytokine promoting eosinophil excess; mepolizumab is a monoclonal antibody against IL-5. In this study, mepolizumab succeeded in reducing eosinophilia in HES while allowing significant reduction of steroid doses. Almost 50% of patients were able to become steroid-free. Anti-IL-5 has not been successful in other disorders associated with eosinophilia, notably asthma, but it may be useful in primary eosinophilic gastrointestinal and pulmonary diseases.*
R. J. M.

Rothenberg ME, Klion AD, Roufosse FE, et al: Treatment of patients with the hypereosinophilic syndrome with mepolizumab.
N Engl J Med. 2008;358:1215-1228. ♦♦

Different Specific IgE Assays Give Varying Results

RADIOALLERGOSORBENT tests (RASTs) such as ImmunoCAP are commonly used to measure specific IgE in patients with food allergies. Changes in food-specific IgE levels over time are used to guide allergy treatment. The ImmunoCAP is not the only assay used for this purpose; different laboratories may use different assays. This prospective study compared IgE measurements with different assays.

The study included deidentified samples from 50 patients in a pediatric allergy practice. Each sample was tested for specific IgE to food and other allergens at different laboratories using different assay systems: ImmunoCAP, Turbo-MP, and Immulite. The equivalence of the IgE results was compared, along with their implications for predicting the clinical probability of reactions to food allergens.

The results showed significant variations between assays. For all allergens, specific IgE levels were higher with Immulite compared to ImmunoCAP. Turbo-MP overestimated egg IgE levels but underestimated those for dust mite and birch pollen. There were also significant variations between ImmunoCAP and Turbo-MP in terms of milk, peanut, and cat allergens, with no trend in either direction. On correlation with clinical data, there was significant variability around decision points that can alter the management of patients with suspected allergy, including discrepancies around the 50% and 95% positive predictive values for clinical reactivity.

Different RASTs may give variable results in measuring specific IgE values, with potential implications for clinical decision making. For patients with food allergy, decision points established by studies using ImmunoCAP do not necessarily apply to measurements made using different assays. Monitoring of specific IgE levels in individual patients over time should use a single assay.

COMMENT: *"A rose is a rose is a rose. . . ." (G. Stein), but a RAST is not a RAST. This study compared three common commercial in vitro assays of specific IgE to several food and environmental allergens, and found that they didn't agree very well. This is important in clinical practice where one is deciding a patient's risk of a serious food reaction on the basis of published data using an assay different from yours. This is not a meaningless distinction. It behooves us to know what our labs are using.*
R. J. M.

Wang J, Godbold JH, Sampson HA: Correlation of serum allergy (IgE) tests performed by different assay systems.
J Allergy Clin Immunol. 2008;121:1219-1224. ♦♦

CHI3L1 Polymorphism Affects YKL-40 Levels, Asthma Risk

PREVIOUS studies have found that patients with asthma have elevated levels of the chitinase-like protein YKL-40, which may be involved in inflammation and tissue remodeling. Circulating levels of YKL-40, which is encoded by the chitinase 3-like 1 gene (*CHI3L1*), have been linked to asthma severity and pulmonary function. Similar associations have been noted for single-nucleotide polymorphisms (SNPs) in the *CHI3L1* promoter associated with high YKL-40 levels. A genomewide association study was done to identify genes affecting serum YKL-40 levels and their effects on asthma and lung function.

The investigators measured serum YKL-40 levels in a founder population of Hutterites, who follow a communal farming lifestyle and rarely smoke. Associations with an implicated *CHI3L1* SNP were tested, along with asthma status and pulmonary function. Genotyping studies for the identified *CHI3L1* variant were then performed in a birth cohort at high risk of asthma, in which serum YKL-40 levels were measured from birth➤➤

through age 5. Genotyping was also done in two populations of asthma case patients and controls.

In the Hutterite population, a -131C → G SNP in the *CHI3L1* promoter was associated with increased serum YKL-40 levels. The same SNP was also linked to the presence of asthma, bronchial hyperresponsiveness, and changes in pulmonary function measures. In the birth cohort, the *CHI3L1* promoter SNP was associated with increased serum YKL-40 levels from birth (cord blood) to age 5. In the case-control populations, the SNP was a significant predictor of asthma: the -131G allele was associated with reduced levels of circulating YKL-40 and about a one-half reduction in asthma risk.

The results identify *CHI3L1* as an asthma susceptibility gene. A specific *CHI3L1* promoter SNP is associated with elevated circulating YKL-40 levels and the presence of asthma, bronchial hyperresponsiveness, and reduced lung function. Larger studies including serum YKL-40 measurement and assessment of asthma status are needed.

COMMENTS: *The search for the "asthma gene" continues, but probably there is no single gene that causes asthma. The latest candidate for an asthma susceptibility gene is one called* CHI3L1, *which stands for "chitinase 3-like 1." This gene codes for a serum protein called YKL-40 (if anyone knows why, please share it with me), the level of which is correlated with asthma severity, thickness of the bronchial basement membrane, and pulmonary function. This study shows that single nucleotide polymorphisms in CHI3L1 affect levels of YKL-40, which are correlated with asthma susceptibility. Someday this kind of information might lead to something important.*
R. J. M.
Ober C, Tan Z, Sun Y, et al: Effect of variation in CHI3L1 *on serum YKL-40 level, risk of asthma, and lung function.*
N Engl J Med. 358:1682-1691. ♦♦

FLG Mutations Linked to Eczema Phenotypes

MUTATIONS of the filaggrin gene (*FLG*) have been linked to eczema and related asthma. Data from a large U.K. population-based birth cohort were used to assess the effects of common *FLG* mutations on eczema, asthma, and other atopic outcomes.

The analysis included approximately 7,000 children born in England during 1990-91, drawn from the Avon Longitudinal Study of Parents and Children. Genotyping studies were performed to identify the two most common null alleles of *FLG*: R510X and 2282del4. The effects of these mutations on the risk of eczema and related asthma were assessed, along with other sensitization outcomes.

The two mutations were associated with an increased prevalence of asthma, as well as with more persistent eczema: the hazard ratio for eczema resolution among subjects with *FLG* mutations was 0.67, compared to those with wild-type *FLG*. The mutations were also associated with an increased risk of asthma, odds ratio 1.80; especially when eczema was present, odds ratio 3.16. Subjects with *FLG* mutations had approximately a twofold increase in sensitization to allergens, including grass, house dust mite, cat dander, and multiple allergens.

Children with *FLG* mutations are at increased genetic risk of eczema, early wheezing, asthma related to eczema, and sensitization to common allergens. They are also less likely to "outgrow" their eczema. Information on *FLG* status could aid risk stratification in children with eczema, including definition of eczema phenotypes associated with early wheezing or asthma.

COMMENT: *In the search for first causes of atopic diseases, the gene that codes for filaggrin,* FLG, *is a leading candidate. Filaggrin is a barrier protein in the stratum corneum of skin, and a deficiency leads to the loss of hydration and increases permeability to allergens, microbes, and irritants. This longitudinal birth-cohort study showed that, in the population of the United Kingdom, polymorphisms in* FLG *correlate with increased odds of developing "eczema with asthma," and can help define children's risk profile.*
R. J. M.
Henderson J, Northstone K, Lee SP, et al: The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study.
J Allergy Clin Immunol. 2008;121:872-877. ♦♦

Early ICS Improves Disease Control in Newly Diagnosed Asthma

IT has been suggested that early treatment with inhaled corticosteroids (ICS) may improve outcomes in patients with newly diagnosed asthma. In the 3-year, double-blind "Inhaled Steroid Treatment As Regular Therapy in Early Asthma" (START) study, early budesonide therapy was associated with a reduction in asthma exacerbations among 7,241 children and adults with mild persistent asthma of recent onset. The results of an open-label extension phase are reported.

The 2-year extension phase included 5,146 patients who were originally assigned to budesonide or switched over from the placebo group. Budesonide dosage was 200 µg for patients less than 11 years old and 400 µg for older patients, added on to usual asthma treatment. The main efficacy variable was change in baseline from postbronchodilator FEV_1 percent predicted.

Across the 5-year study period, there was an average 2.22% decrease in postbronchodilator percent predicted FEV_1. This was so regardless of whether patients were initially assigned to budesonide or placebo. However, the risk of severe asthma-related events was significantly lower for patients randomized to budesonide, odds ratio 0.61. Differences in symptom-free days were no longer significant during open-label treatment with budesonide. Patients in the original placebo group used more additional asthma medications during both the double-blind and extension phases.

Five-year results of the START study show beneficial effects of early ICS therapy for patients with ➤➤

recent-onset asthma. Observations in patients started on budesonide after 3 years on placebo suggest that early ICS therapy is associated with better disease control and less need for additional asthma medications. The results support current guidelines calling for daily ICS therapy for adult and pediatric patients with mild persistent asthma.

COMMENT: *Whether to start ICS as first-line treatment of recent-onset mild persistent asthma is still debated. This large (7,241 patients) longitudinal (5 years) study showed that the early institution of ICS improved clinical outcomes such as occurrence of severe asthma episodes and decreased the need for additional asthma medications. The latter effect continued even in the open-label period, during which the non-ICS subjects were transferred to ICS for two years. However, there was no improvement in post-bronchodilator FEV_1 in the treated group. This study seems to corroborate other data that indicate that ICS improve clinical asthma control but don't favorably affect long-term pulmonary function.*
R. J. M.

Busse WW, Pedersen S, Pauwels RA, et al: The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma.
J Allergy Clin Immunol. 2008;121:1167-1174. ♦♦

HDI Exposure Produces Innate Immune Responses

ISOCYANATES, used in the production of polyurethane, are an important cause of occupational asthma. These highly reactive chemicals produce well-recognized adaptive immune responses. However, little is known about their potential for innate immune responses, which typically occur first and regulate adaptive immunity. Innate immune responses induced by exposure to hexamethylene di-isocyanate (HDI) were studied in detail.

In in vitro studies, human peripheral blood monocytes (PBMCs) were stimulated with HDI-albumin conjugates or control antigens. After taking up the HDI-albumin conjugates, the monocytes showed significant changes in morphology and gene/protein expression. Lysosomal genes, particularly peptidases and proton pumps involved in antigen expression, were especially affected. Increases in chemokines regulating monocyte/macrophage trafficking and pattern-recognition receptors binding chitin and oxidized low-density lipoprotein were observed as well.

In in vivo experiments, human subjects underwent a specific HDI inhalation challenge. Exposure to HDI was associated with a sharp increase in PBMCs with the same HDI-albumin responsive phenotype seen in the in vitro studies. In subjects with a gene polymorphism associated with a lack of type 1 human chitinase, there was an exposure-dependent 46% decrease in serum chitinase 3-like-1 level. No such change was seen in subjects who had at least one functional chitinase-1 allele.

Hexamethylene di-isocyanate and HDI-albumin conjugates induce previously unrecognized innate immune responses in humans. These responses could play an important role in the development of occupational allergies to this isocyanate chemical. Genetic variations in innate immune responses may help to explain individual variations in the outcomes of HDI-exposed workers, as well as the differences between isocyanate asthma and typical atopic asthma.

COMMENT: *Isocyanate exposure is an important cause of occupational asthma and serves as a classic example of a "low molecular weight" sensitizer. This study provides evidence that isocyanates activate the innate arm of the immune system, which may help explain the clinical spectrum of isocyanate-induced disease.*
S. A. T.

Wisnewski AV, Liu Q, Liu J, Redlich CA: Human innate immune responses to hexamethylene diisocyanate (HDI) and HDI-albumin conjugates.
Clin Exp Allergy. 2008;38:957-967. ♦♦

What Are the Best Sites for SLIT?

IN effective responses to sublingual immunotherapy (SLIT), oral Langerhans cells (LCs) may play an important role as antigen-presenting cells. In contrast, oral mast cells may be involved in oral itching and submucosal edema, which are important adverse reactions to SLIT. Toward identifying optimal application sites for SLIT, the investigators analyzed the distribution of LCs and mast cells within the oral mucosa.

Punch biopsy specimens were obtained from various sites in the oral mucosa and from epidermal skin in autopsy subjects. The distribution of LCs, mast cells, and high-affinity receptor for IgE (FcεRI) expression of LCs was studied by immunohistochemistry and flow cytometry. T-cell proliferation assays were performed to study the stimulatory capacity of cells from different locations.

Mast cell density was highest in the gingiva and lowest in the palatal and lingual areas. Mast cells were also found within the lobes and ducts of sublingual glands, which might help to explain reports of swelling of the sublingual caruncle after SLIT. The vestibular region had the highest density of LCs, while the sublingual region had the lowest density.

Vestibular LCs had the greatest expression of FcεRI. Stimulatory capacity in response to allogeneic T cells was similar for LCs in different regions.

The distribution of LCs and mast cells in the oral mucosa may have implications for SLIT application. For example, because of the high LC density and FcεRI expression in the vestibular or buccal area, these sites might enhance allergen uptake from SLIT.

COMMENT: *Although high-dose SLIT impressively improves respiratory allergy symptoms, there is a high rate of local side effects such as oral itching. By demonstrating anatomic variations in the relative number of LCs and mast cells in the oral mucosa, this* ➤➤

study paves the way for refining the SLIT technique to optimize tolerance induction and minimize local side effects.
S. A. T.
Allam J-P, Stojanovski G, Friedrichs N, et al: Distribution of Langerhans cells and mast cells within the human oral mucosa: new application sites of allergens in sublingual immunotherapy?
Allergy. 2008;63:720-727. ♦♦

What's New on Asthma in Elite Athletes?

ELITE athletes have high rates of asthma. More and more young athletes show evidence of IgE-mediated allergy--this, along with participation in endurance sports, is a major risk factor for asthma. Recent findings on asthma in elite athletes are summarized, including the features of two well-characterized groups of Olympic athletes.

The report includes an analysis of the clinical features of all asthmatic athletes on the Finnish Olympic team, as well the British Olympic swimming team. The Finnish sample showed two distinct clinical phenotypes, which may have different underlying mechanisms. One group of athletes had a "classic asthma" pattern, with childhood onset, methacholine responsiveness, atopy, eosinophilic airway inflammation, and high exhaled nitric oxide. The other group had late-onset asthma, with symptoms developing during the athletes' sports career. The latter group had bronchial responsiveness to eucapnic hyperventilation, but not always to methacholine; atopic markers and exhaled nitric oxide were variable.

Especially among swimmers, ice-hockey players, and cross-country skiers, there was evidence that allergic and irritant mechanisms contributed to a mixed pattern of eosinophilic and neutrophilic airway inflammation. The prevalence of asthma on the British Olympic swimming team was 40% or higher. The mechanisms of asthma among elite swimmers were complex, possibly including chemical exposures, microaspiration of water droplets, hyperventilation, and autonomic dysregulation.

In elite athletes, there is real potential for overdiagnosis of asthma. Objective testing is essential; the criteria for allowing inhaled beta-2 agonist use by Olympic athletes are stringent. Overtreatment is possible as well, and may reduce the ability of medications to prevent and treat exercise-induced bronchoconstriction. Follow-up studies are needed to clarify the temporal relationship between asthma and competitive sports, including better assessment of environmental factors, training intensity, and potential confounders.

COMMENT: *Prolonged intense exercise is thought to play a role in the pathogenesis of asthma in some athletes, and the prevalence of asthma in elite endurance athletes is alarmingly high. For example, in the 2004 Olympics 44% of the swimmers from Great Britain had asthma. This excellent review summarizes data collected on Finnish Olympic athletes and also extensively discusses exercise-induced asthma in swimmers. The authors also acknowledge the very real risk of overdiagnosis and overtreatment of asthma in elite athletes.*
S. A. T.
Haahtela T, Malmberg P, Moreira A: Mechanisms of asthma in Olympic athletes--practical implications.
Allergy. 2008;63:685-694. ♦♦

Nasal Allergen Challenge Leads to Sinus Inflammation

A possible link between allergic rhinitis and chronic rhinosinusitis is supported by the findings of positive skin test results in at least half of patients with rhinosinusitis and high rates of sinus disease among patients with allergic rhinitis. This study examined the effects of nasal allergen challenge on sinus inflammation, including the effect of antihistamine pretreatment.

The randomized crossover trial included 20 patients with seasonal allergic rhinitis, studied out of season. Subjects received 1 week of treatment with loratadine, 10 mg/d, or placebo. After lavage of the maxillary sinus, nasal challenge was performed using three concentrations of grass or ragweed or with diluent. Nasal and sinus lavages were performed for up to 8 hours after challenge, with measurement of eosinophils, eosinophil cationic protein, albumin, and histamine. Challenges using lactated Ringer's solution were performed in a subset of 11 patients.

The nasal specimens showed increases in most early- and late-phase indicators after allergen challenge, compared with lactated Ringer's challenge. Nasal allergen challenge was also associated with increases in eosinophil count in the maxillary sinus, as well as in albumin, eosinophil cationic protein, and histamine during the late phase. Early nasal responses to allergen challenge were significantly reduced in patients pretreated with loratadine.

In patients with seasonal allergic rhinitis, nasal allergen challenge results in inflammatory changes within the maxillary sinus. This response could be explained by systemic inflammation and/or a neurogenic reflex between the nose and sinus. Regardless of the mechanism, the findings may help to explain the association between allergic rhinitis and rhinosinusitis.

COMMENT: *In this carefully designed study, nasal allergen challenge triggered maxillary sinus inflammation. Interestingly, antihistamine treatment inhibited the early nasal response but not the late responses in either the nose or the sinus. The authors suggest that a neural reflex may be at least partially responsible for this nasosinus response. This helps explain the link between rhinitis and chronic sinusitis.*
S. M. F.
Baroody FM, Mucha SM, deTineo M, Naclerio RM: Nasal challenge with allergen leads to maxillary sinus inflammation.
J Allergy Clin Immunol. 2008;121:1126-1132. ♦♦

Overweight-Asthma Link Begins in Infancy

MANY reports have noted a direct association between increased body mass index and the risk of asthma, wheezing, and airway hyperresponsiveness in children. These studies have focused on school-age or older children, whereas the peak incidence of asthma occurs at younger ages. A measure of infant adiposity was evaluated as a predictor of recurrent wheezing in early childhood.

The analysis included 932 children from a prospective cohort study. All had available data on weight-for-length (WFL)--a proxy measure of adiposity--at age 6 months. Rates of recurrent wheezing through age 3 were assessed by parental report; other wheezing and asthma outcomes were assessed as well. Multiple logistic regression analysis was performed to assess the relationship between WFL z scores at 6 months with early childhood wheezing and asthma.

The median WFL z score at age 6 months was 0.68, with a range of -2.96 to 3.24. The rate of recurrent wheezing by age 3 was 14%. On adjusted analysis, infants with higher WFL z scores were at higher risk of early childhood wheezing. For each one-unit increase in 6-month WFL z score, odds ratios were 1.46 for recurrent wheezing and 1.23 for any wheezing. A positive association with WFL z score and asthma was nonsignificant.

Infants with higher adiposity at age 6 months are at greater risk of recurrent wheezing by age 3 years. For a male infant of average length, a 0.4 kg increase in body weight is associated with nearly a 50% increase in the risk of recurrent wheezing, the investigators calculate. Measures to prevent infant adiposity might influence the risk of asthma symptoms later in childhood.

COMMENT: *Infant WFL measurement is considered a surrogate for adiposity in infants and children less than 2 years old. The findings of this prospective cohort study suggest that infants who are overweight at 6 months have a greater risk of wheezing by age 3 years. Even a one-unit difference in WFL, which is calculated from a 0.7 kg weight difference, could result in a 46% greater risk of wheezing. This study suggests another reason to take precautions against childhood obesity.*
S. M. F.

Taveras EM, Rifas-Shiman SL, Camargo CA Jr, et al: Higher adiposity in infancy associated with recurrent wheeze in a prospective cohort of children.
J Allergy Clin Immunol. 2008;121:1161-1166. ♦♦

Overweight May Not Increase Asthma Risk in Asian-Americans

DATA from several sources, including the National Health and Nutrition Examination Study (NHANES), have suggested an association between overweight and childhood asthma. Most of these studies have focused on white or African-American children. This study looked at the relationship between body mass index (BMI) and asthma in Asian-American children.

The case-control study included 94 Asian patients, aged 4 to 18 years, with a physician diagnosis of asthma. Mean age at asthma diagnosis was 6.11 years. Ninety-four Asian children without asthma served as controls. The BMI of asthmatic children, before and after asthma diagnosis, was compared with that of the nonasthmatic controls.

The asthmatic and nonasthmatic Asian-American children were not significantly different in terms of BMI and BMI percentile. This was so for boys, girls, and both sexes combined. Cases and controls were similar in the percentage of children in each weight category (underweight, normal weight, at risk of overweight, and overweight). Linear trends before and after asthma diagnosis were also similar between groups.

This study finds no relationship between BMI and asthma risk among Asian-American children. The reasons for this finding are unknown, but might involve differences between the traditional Chinese diet and the Western diet.

COMMENT: *This study argues against an association between obesity and asthma, suggesting that there may be some ethnic differences in the relationship between body mass index and asthma or asthma severity. Many other studies have shown a weight/asthma correlation, so this information may not be accurate. Nevertheless, these observations may lead us to question the connection in all populations. Furthermore, the most recent NHANES data show that the increase in obesity and excess weight in children has plateaued, albeit at 17% and 30% of the general pediatric population (see JAMA 2008;299:2401-05).*
D. K. L.

Henkin S, Brugge D, Bermudez OI, Gao X: A case-control study of body mass index and asthma In Asian children.
Ann Allergy Asthma Immunol 2008;100:445-451. ♦♦

Is Neonatal Antibiotic Use a Risk Factor for Wheezing?

ANTIBIOTIC treatment during the first year of life has been studied as a risk factor for childhood asthma. However, the potential for reverse causation--that children with asthma symptoms might receive more antibiotics--complicates research of this issue. To minimize the risk of reverse causation, this study examined the relationship between neonatal antibiotic treatment and risk of early wheezing.

The analysis included data on 4,921 infants from a Swedish birth cohort study. Wheezing symptoms were assessed by parental questionnaires at 6 and 12 months; response rates were around 70% at both times. Treatment with antibiotics while on the neonatal ward was analyzed as a risk factor for early wheezing in multivariate models.

By 12 months, at least one episode of wheezing was reported for 20.2% of infants and three or more episodes by 5.3%. Treatment with inhaled corticosteroids was reported for 4.1% of infants. Neonatal ➤➤

antibiotic treatment was an independent risk factor for wheezing before age 1, odds ratio 1.8. Other significant factors were male sex, gestational age less than 37 weeks, maternal history of asthma, history of asthma or eczema in siblings, and breast-feeding for less than 5 months.

Infants who receive antibiotics in the neonatal ward show an 80% increase in the risk of wheezing during the first year of life. The association might be explained by a change in the intestinal flora related to neonatal antibiotic treatment. Further studies, including detailed information on neonatal antibiotic administration, are needed.

COMMENT: *The authors of this large, retrospective study from Sweden postulate that use of antibiotics early in life independently increases the risk of wheezing, consistent with the hygiene hypothesis. To reduce the likelihood of reverse causation, neonatal rather than infant antibiotic use was assessed. Nonetheless, with recent data suggesting that even transient tachypnea of the newborn may be a precursor to wheezing symptoms (see J Pediatr. 2007;151:29-33), one wonders whether reverse causation might remain an issue.*
K. R. M.

Alm B, Erdes L, Möllborg P, et al: Neonatal antibiotic treatment is a risk factor for early wheezing.
Pediatrics. 2008;121:697-702. ♦♦

CLINICAL TIDBITS

Lactobacillus GG Does Not Prevent Atopic Dermatitis

THERE is ongoing debate over the role of probiotics for the prevention of asthma and allergic disease. One previous randomized, placebo-controlled trial found a significant reduction in atopic dermatitis among infants receiving the probiotic strain *Lactobacillus* GG. The current study attempted to replicate those results in a sample of 105 pregnant women with a family history of atopic disease.

In double-blind fashion, one group received *Lactobacillus* GG, starting 4 to 6 weeks before delivery and continuing to postnatal age 6 months. By age 2, atopic dermatitis had been diagnosed in 28.0% of infants assigned to probiotic supplementation, compared with 27.3% of the placebo group. There was also no difference in atopic dermatitis severity.

Five or more episodes of wheezing bronchitis were reported in 26.0% of children in the *Lactobacillus* GG group compared with 9.1% of controls. There were no significant differences in total IgE or sensitization to inhalant allergens.

This trial finds no benefit of *Lactobacillus* GG supplementation in primary prevention of atopic dermatitis. Instead, probiotic treatment may be associated with an increased rate of recurrent episodes of wheezing bronchitis.

COMMENT: *The hygiene hypothesis postulates that changes in gastrointestinal flora at an early age lead to alteration in T-cell development and promote atopic disease. Questions have been reasonably raised about whether altering this flora prospectively may lead to more normal T-cell development, thereby preventing disease. A single, positive (preventive) double-blind placebo-controlled (DBPC) study of atopic dermatitis has been noted previously. The current prospective DBPC study, which replicates the methodology of that prior study, adds to the growing evidence that probiotics do not alter the course of atopy. Of concern in this particular study--and of unclear etiology--is the significant increase in wheezing episodes seen in the group receiving* Lactobacillus *GG.*
K. R. M.

Kopp MV, Hennemuth I, Heinzmann A, Urbanek R: Randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: no clinical effects of Lactobacillus *GG supplementation.*
Pediatrics.2008;121:e850-e856. ♦♦

IL-4 Gene Polymorphism Plus ETS Increases Wheezing in Black Infants

SINGLE-nucleotide polymorphisms of interleukin (IL)-4 and IL-13 could be genetic factors affecting asthma risk, possibly in interaction with environmental factors like passive smoking. Exposure to environmental tobacco smoke (ETS) and IL-4 and IL-13 polymorphisms were evaluated as risk factors for wheezing in infants with a family history of atopy.

Genotyping for the C-589T polymorphism of IL-4 and the C-1112T polymorphism of IL-13 was performed in 560 of a birth cohort of 758 infants. At a mean age of 13.4 months, 29.0% of infants had allergic sensitization and 26.2% had wheezing without a cold. Among African-American infants, the combination of ETS exposure and the CT/TT genotypes for IL-4 C-589T was associated with a greatly increased risk of wheezing: odds ratio 10.84. This interaction was not significant for non-African-American infants.

Among African-American infants with a family history of atopy, an interaction of ETS exposure and an IL-4 polymorphism is related to an increased risk of wheezing during the first year of life. In this group of genetically susceptible infants, efforts to avoid ETS exposure might significantly reduce the rate of asthma symptoms.

COMMENT: *Exposure to ETS is clearly deleterious to children with respiratory disorders, but certain populations may be disproportionately affected. This study sheds light on a possible mechanism for increased wheezing in African-American infants exposed to ETS. Extrapolation of these results will require additional study, as only 14 African-American children in the study were exposed to higher levels of ETS; the significant finding comes from a subset of this sample. Counterintuitively, analysis of non-African-American infants with the same IL-4 polymorphism and higher ETS did not yield a similar result.*
K. R. M. ➤➤

Smith AM, Bernstein DI, LeMasters GK: Environmental tobacco smoke and interleukin 4 polymorphism (C-589T) gene: environment interaction increases risk of wheezing in African-American infants.
Pediatrics. 2008;152:709-715. ♦♦

Study Looks at Progression from Selective IgAD to CVID

SELECTIVE IgA deficiency (IgAD) is the most common primary immunodeficiency disorder in whites. This condition is frequently asymptomatic, although some patients have increased rates of infections, allergies, and autoimmune signs and symptoms. Because combined variable immunodeficiency (CVID) shares many characteristics with IgAD, a common genetic cause has been suggested.

The authors report on four patients from Sweden, Iran, and Spain with IgAD and autoimmune features who went on to develop CVID. They also review the previously reported findings of another 20 IgAD patients who progressed to CVID.

The patients underwent HLA typing for HLA A, B, DR and DQ loci by sequence-specific primed polymerase chain reaction. Analysis of the TNFRSF13B gene for disease-associated single-nucleotide polymorphisms (SNPs) was performed as well. No mutations in the disease-associated C104R, A181E, and R202H SNPs of *TNFRSF13B* were found. However, significant associations were noted for HLA A1, B8, DR3, DQ2.

COMMENT: *This study of patients with selective IgAD progressing to CVID suggests that associations of HLA A1, B8, DR3, DQ2, or part of this haplotype in affected family members, could be risk factors for induction of CVID. All symptomatic patients with IgAD should be carefully monitored for possible progression to CVID. Family studies in such a group of patients were also suggested.*
M. F.
Aghamohammadi A, Mohammadi J, Parvaneh, N et al: Progression of selective IgA deficiency to common variable immunodeficiency.
Int Arch Allergy Immunol. 2008;147:87ñ92. ♦♦

HLA Class I and II Alleles in Chronic Urticaria

RECENT data suggest an autoimmune component in up to one-third of patients with chronic urticaria (CU). In about 30% of cases, CU is associated with a histamine-releasing anti-Fcε RIα autoantibody.

This study looked at the association between HLA class I and class II antigens and the immune pathogenesis of CU. Serologic techniques and polymerase chain reactions were used to study HLA class I and class II antigens in 40 patients with CU and about 30 unrelated individual controls. The frequency of HLA-B44 was 25% among CU patients versus 3.33% in controls.

On HLA class II genotyping, HLA-DRB1*01 and HLA-DRB*15 were found in 25% of CU patients. These findings support the theory that genetic factors play a role in the development of CU.

COMMENT: *This study investigated the relationship between HLA class I and class II antigens and immune pathogenesis of CU. HLA-B44 frequency was significantly higher in the patients as compared with the matched controls, but there was no significant difference in HLA-A allelic distribution. In the genotyping of class II HLA alleles, HLA-DRB1*01 and HLA-DRB*15 were the predominant alleles. The authors concluded that the association of HLA-B44, HLA DRB1*01, and HLA-DRB*15 alleles with idiopathic CU suggests a genetic component in the pathogenesis of CU.*
M. F.
Çoban M Erdem T, Özdemir S, et al: HLA class I and class II genotyping in
patients with chronic urticaria.
Int Arch Allergy Immunol. 2008;147:135-139. ♦♦

For Selected Patients, Open Food Challenges Are Safe

IN clinical assessment of patients with suspected food allergies, open food challenges provide an alternative to double-blind placebo-controlled food challenges. A 3-year experience was reviewed to evaluate the safety of performing open food challenges in the office setting.

The experience including 109 patients undergoing pen food challenges in a university pediatric allergy clinic during 2001-04. A total of 150 challenges were performed, most commonly involving milk, peanut, and egg. There were 40 positive challenges, a rate of 27%, in 33 patients.

Ninety-two percent of the reactions to open food challenge were mild to moderate. Of the positive challenges, cutaneous reactions were involved in 68%, gastrointestinal reactions in 45%, and upper respiratory (nonlarygneal) reactions in 38%. In 92% of challenges, management consisted of observation or antihistamines only; in no case was epinephrine or hospitalization required.

The severity of reactions was unrelated to specific IgE levels. However, the patients with negative reactions to milk, peanut, and egg had food-specific IgE levels around the published negative predictive values. In 88 patients, negative challenges led to the introduction of 19 different foods.

This experience supports the safety of office-based open food challenges for selected patients. Patient selection for open challenge is based on the history of food-specific IgE level.

COMMENT: *Double-blind, placebo controlled food challenges are generally not practical for busy, outpatient clinics and offices. Open challenge is a useful means of reassuring a patient or patientís family of the safety of a specific food. This experienced group provides data demonstrating an open challenge is safe and reasonable, assuming the history and testing results are consistent with the population reported in this paper.* ➤➤

D. K. L.
Mankad VS, Williams LW, Lee LA, et al: Safety of open food challenges in the office setting.
Ann Allergy Asthma Immunol. 2008;100:469-474. ♦♦

Which Test Is Best for Mouse Allergy?

THE optimal test for clinically relevant sensitization to mouse is unclear. This study compared the results of skin tests and mouse-specific IgE levels in laboratory workers. Of 69 workers tested, 49 reported mouse-related symptoms. After skin-prick testing (SPT), intradermal testing (IDT), and specific IgE measurement, all workers underwent nasal challenge with mouse allergen. The mouse extract used for skin testing was from a single lot of commercially available extract (Greer Labs 1:10 W/V).

Of 49 workers reporting symptoms, 10 had positive mouse-specific IgE levels and 12 had positive SPTs. In 15 cases, IDT was positive while SPT was negative. Rates of positive responses to nasal challenges were 70% for workers with positive specific IgE results, 83% for those with positive SPTs, 33% for those with negative SPT but positive IDT, and 0% for those with negative IDTs.

Skin-prick testing offers the highest positive and negative predictive value for assessment of mouse allergy in laboratory workers, compared to mouse-specific IgE measurement and IDT. Positive reactions to nasal mouse allergen challenge are associated with increased nasal eosinophliia.

COMMENT: *Skin prick tests were best at determining which lab workers had clinically significant mouse allergy. The sensitivity for in vitro mouse-specific IgE was only 47% compared to 67% for SPT, along with a specificity of 94%. No glycerin was used in the IDTs to avoid potential irritant reaction. Once again, SPTs are found to be the gold standard for determining clinically significant allergic disease.*
S. M. F.
Sharma HP, Wood RA, Bravo AR, Matsui EC: A comparison of skin prick tests, intradermal skin tests, an specific IgE in the diagnosis of mouse allergy.
J Allergy Clin Immunol. 2008;121:933-939. ♦♦

REVIEWS OF NOTE

COMMENT: *This is a well-written update that combines a thorough review of the literature with the practical observations of an experienced, academic allergist/immunologist. I highly recommend.*
D. K. L.
Morgan M, Khan DA: Therapeutic alternatives for chronic urticaria: an evidence-based review, part 1.
Ann Allergy Asthma Immunol. 2006;100:403-412. ♦♦

COMMENT: *These two papers are not exhaustive reviews but focus on cough as it pertains to asthma, eosinophilic bronchitis, and other etiologies. The authors propose a different* zeitgeist *with regard to cough, which emphasizes looking at cough pathways. Implications for new treatment approaches are presented.*
S. F. W.
Chung KF, Pavord ID: Chronic cough 1: prevalence, pathogenesis, and causes of chronic cough. Lancet. 2008;371:1364-1374; and Pavord ID, Chung KF: Chronic cough 2: management of chronic cough.
Lancet. 2008;371:1375-1384. ♦♦

COMMENT: *This is an excellent review, presented by one of our own.*
S. F. W.
Burks AW: Peanut allergy.
Lancet. 2008;371:1538-1546. ♦♦

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