AllergyWatch®

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

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Vital Advances on Peanut Allergy

PEANUT allergy is a common and potentially lethal problem. The only available treatments are avoidance, which is difficult; and rescue medication with epinephrine. The anti-IgE monoclonal antibody TNX-901 demonstrates high-affinity binding to an epitope in the CH_3 domain, a region involving binding to FcεRIs and low-affinity Fcε receptors. This study reports the clinical effects of anti-IgE therapy with TNX-901 for peanut allergy.

The multicenter randomized, controlled trial included 84 patients with immediate hypersensitivity reactions to peanut allergy. All patients, aged 12 to 60 years, had a history of urticaria, angioedema, lower respiratory tract symptoms, or hypotension in response to peanut exposure. At baseline, patients underwent randomized double-blind oral food challenge to establish their threshold value for hypersensitivity symptoms to peanut flour. They were then randomized into three TNX-901 dosage groups--150, 300, or 450 mg subcutaneously--and a placebo group. Each group was treated every 4 weeks for four doses. Final outcomes were assessed 8 weeks after the last dose of study medication; adverse effects were monitored throughout. The main outcome measure was change in threshold dose inducing a reaction to peanut flour.

Ninety-two percent of peanut challenges induced a typical moderate to severe reaction. Patients receiving the 450 mg dose of TNX-901 had a significant increase in the threshold for sensitivity to peanut challenge. For this group, the threshold value increased from 178 mg at baseline to 2,805 mg at follow-up. Thus their ability to tolerate peanut exposure increased from about one-half peanut to nearly nine peanuts. Monitoring of serum free IgE levels showed significant reductions from baseline in all three TNX-901 groups: by 72% at the 150 mg dose, 79% at the 300 mg dose, and 89% at the 450 mg dose.

For patients with peanut allergy, anti-IgE therapy with TNX-901 significantly increases the threshold for sensitivity reactions to oral peanut challenge. At the higher doses studied, TNX-901 therapy should offer protection against most inadvertent peanut ingestions. ➤➤

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

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

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COMMENT: *Currently there is no effective treatment for peanut allergy, which occurs in about 1.5 million Americans and kills 50 to 100 per year. Avoidance is difficult. TNX-901 is a humanized monoclonal anti-IgE that reduces unbound circulating IgE and, perhaps more importantly, causes substantial down-regulation of IgE receptors on basophils (and presumably mast cells). Treatment with this anti-IgE was found to raise the threshold for reactions to oral peanut challenges to a level approximating eight or nine whole peanuts.*
R. J. M.

Leung DYM, Sampson HA, Yunginger JW, et al, for the TNX-901 Peanut Allergy Study Group: Effect of anti-IgE therapy in patients with peanut allergy.
N Engl J Med 348:986-983, 2003. ♦♦

ATOPY and family history have been identified as risk factors for peanut allergy. However, studies of other potential risk factors--including maternal consumption of peanuts during gestation and ingestion of soy milk by infants--have yielded conflicting results. Data from a population-based cohort study were used to evaluate risk factors for development of peanut allergy in young children.

Subjects were drawn from the Avon Longitudinal Study of Parents and Children, which included nearly 14,000 preschool-aged children in one U.K. health district. Based on questionnaire responses, 49 children with a clear history of hypersensitivity reactions to peanut were identified. Of 36 children tested, 29 had a positive reaction to skin testing and 23 had a positive reaction to double-blind peanut challenge. Potential risk factors were evaluated by analyzing prospective and retrospective interview responses from parents. Children with reactions to peanut were compared with two control groups: a random sample from the overall cohort and a group of children whose mothers had a history of eczema and who had eczema themselves during infancy.

On analysis of prospective interview data, peanut allergy was unrelated to any of the socioeconomic factors studied or exposure to environmental tobacco smoke. However, a positive reaction to peanut challenge was significantly associated with maternal history of atopy, specific allergies, or asthma. The study found no evidence of prenatal sensitization to peanut--no peanut-specific IgE was detected in cord blood samples. Independent risk factors for peanut allergy were ingestion of soy milk or soy formula; rashes over skin joints or creases; and oozing, crusting rashes.

Information from the detailed, retrospective interviews suggested that children with peanut allergy had high rates of exposure to skin creams containing peanut oil during infancy. Children with peanut allergy were exposed to about twice as many peanut oil-containing products than those in the control groups, including the atopic controls.

The results suggest a possible cutaneous route of the development of childhood peanut allergy: application of peanut oil-containing products to inflamed skin during infancy. The implicated products are mainly emollients used to treat diaper rash, eczema, dry skin, and other inflammatory skin conditions of infancy. Ingestion of soy products during infancy is also an independent risk factor, possibly reflecting cross-sensitization. The study finds no evidence that peanut allergens are transmitted in breast milk.

COMMENT: *It has long been thought that food allergy contributes to the development of atopic dermatitis. This study suggests exactly the opposite: inflammatory skin conditions might allow penetration of food proteins, such as peanut and soy proteins, contained in emollients, resulting in food allergy. The researchers found no evidence of sensitization in utero and no protective effect of breast-feeding. The findings support the notion that broken skin exposed to products containing peanut antigens may be the route of sensitization to peanuts.*
R. J. M.

Lack G, Fox D, Northstone K, Golding J, for the Avon Longitudinal Study of Parents and Children Study Team: Factors associated with the development of peanut allergy in childhood.
N Engl J Med 348:977-985, 2003. ♦♦

Most Latex-Allergic Health Care Workers Have Good Occupational Outcomes

SENSITIZATION to natural rubber latex (NRL) is a common occupational allergy among health care workers. With the high frequency of this problem and the likelihood of exposure to ambient allergens in health care settings, NRL allergy could be a major cause of work-related illness and disability. Occupational outcomes of a series of health care workers with NRL allergy were assessed.

The study included 67 health care workers with NRL allergy, confirmed by percutaneous reactivity to nonammoniated latex. The subjects had been recruited for a study of an in vivo skin prick test for NRL allergy; those with unstable asthma or a baseline FEV_1 of less than 70% predicted were excluded. In response to a questionnaire, the workers provided information on their clinical symptoms in response to NRL glove exposure, environmental interventions made after their allergy was recognized, and the outcomes of those interventions. The disorders of interest were work-aggravated contact urticaria, with or without rhinitis, asthma, or anaphylaxis.

The workers were 64 women and 3 men, mean age 36 years. They had worn NRL gloves for a mean of 5 years before developing allergic symptoms. All workers initially had work-aggravated urticaria, usually accompanied by other symptoms. Of 15 workers with contact urticaria only, 11 switched to non-NRL gloves. All of these patients had complete resolution of work-related hives. Eighteen workers with work-related rhinitis and contact urticaria switched to non-NRL gloves. Symptoms resolved in 15 of these.

Of 25 workers with work-aggravated asthma, 19 switched to non-NRL gloves. Symptoms resolved in 18 of these subjects, even though most of them continued to work with colleagues who wore powdered latex gloves. However, 4 workers with asthma symptoms had persistent symptoms, forcing them to change either their work area or place of employment. Of 4 subjects with anaphylactic symptoms, 3 had no further problems after moving to an NRL-free environment within the same facility.

Most health care workers with NRL allergy have good occupational outcomes. Cutaneous symptoms and rhinitis generally resolve after the worker switches to non-NRL gloves. However, health care facilities may be less likely to accommodate workers with symptoms of occupational asthma.

COMMENT: *This paper provides a reassuring picture of the long-term results of personal avoidance of NRL by health care workers, despite their remaining in a health care environment with some degree of ambient latex exposure. The authors discuss potential selection biases that could, but probably do not, limit the general applicability of their findings. In general, health care workers with NRL allergy should be encouraged to remain in their jobs and avoid the personal use of latex gloves. Disability or job change is the uncommon exception, not the rule.*

D. K. L.

Bernstein DI, Karnani R, Biagini RE, et al: Clinical and occupational outcomes in health care workers with natural rubber latex allergy.

Ann Allergy Asthma Immunol 90:209-213, 2003. ♦♦

Pilot Study Supports IV Montelukast for Acute Asthma

EMERGENCY department visits for asthma are a major problem for pediatric and adult patients alike. Given orally, the leukotriene receptor antagonist montelukast is of demonstrated benefit in the management of chronic asthma. The use of intravenous montelukast for patients with acute asthma was evaluated in a pilot study.

A total of 201 adult patients with moderate to severe acute asthma were enrolled at 16 U.S. centers. Those with FEV_1 of greater than 70% predicted were excluded. All patients received standard treatment. In addition, they were randomized to receive intravenous montelukast, 7 or 14 mg, or matching placebo. The main study outcome was average percentage change in FEV_1 at 20 minutes after the study medication.

The two groups were similar in their clinical and other baseline characteristics. Mean percentage increase in FEV_1 was 14.8% for patients in the montelukast groups, compared with 3.6% in the placebo group. The benefits of montelukast appeared within 10 minutes after administration and were still present after 2 hours. Compared with the placebo group, patients receiving intravenous montelukast used lower amounts of β-agonists and had a somewhat lower treatment failure rate.

For adult patients with acute asthma, intravenous montelukast provides prompt improvement in FEV_1, when added to standard therapy. This treatment is well tolerated and may lead to improvements in other clinical outcomes as well.

COMMENT: *Questions have been repeatedly raised about the role of leukotrienes in acute asthma and the potential value of a leukotriene receptor antagonist as asthma therapy in acute clinical settings. This pilot study looked at intravenous montelukast as an add-on for acute asthma in placebo-controlled fashion. Results demonstrated a significant and rapid response to IV montelukast, suggesting a possible role of leukotriene receptor antagonists in the acute management of asthma exacerbations.*

G. D. M.

Camargo CA, Smithline HA, Malice M-P, et al: A randomized controlled trial of intravenous montelukast in acute asthma.

Am J Respir Crit Care Med 167:528-533, 2003. ♦♦

Steroid Bursts Don't Cause Lasting Disruptions of Bone and Adrenal Status in Asthmatic Children

PHYSICIANS and parents worry about side effects of repeated courses of oral glucocorticoids to treat asthma exacerbations in children, especially osteopenia and adrenal suppression. The effects of repeated "bursts" of oral glucocorticoids on bone mineralization and metabolism and adrenal function were assessed in asthmatic children.

The cross-sectional study included 83 children, aged 2 to 17 years, seen for acute asthma exacerbations. Of these, 48 had received two or more short courses of oral glucocorticoids during the preceding year--median four courses--and received the same treatment for the index exacerbation. The remaining 35 children had no exposure to oral glucocorticoids, including for the index exacerbation. Markers of bone metabolism, bone density, and cortisol responses to adrenocorticotropic hormone stimulation were compared between the exposed and unexposed groups.

The exposed children had a higher frequency and severity of exacerbations. Bone metabolism studies showed a 30% reduction in baseline serum osteocalcin in the exposed group, which returned to baseline by 30 days. Urine pyridinoline did not differ significantly between groups. After 30 days, bone density measurements were not significantly different, but were lower than reference values for age, sex, and race. There were also no differences in basal and peak cortisol responses to adrenocorticotropic hormone.

Repeated bursts of oral glucocorticoids cause transient abnormalities of bone deposition in children with asthma. However, a month after the end of therapy, measures of bone mineralization, bone deposition, and adrenal function are no different than in children with asthma not receiving glucocorticoid bursts.

COMMENT: *This study reassures clinicians that short oral corticosteroid bursts may be okay in children with asthma. Up to four oral corticosteroid bursts did not appear to alter bone formation or adrenal function in the long term. It is hoped that this study will not lead to complacency when it comes to treating asthma. In a recent study of over 30,000 asthmatics, also from McGill University, low-dose inhaled corticosteroids prevented a significant number of asthma hospitalizations initially and in the long term (*Thorax *57:880-884, 2002; see* AllergyWatch *Jan.-Feb. 2003). The take-home message: use daily protective medications for asthma to help prevent the most serious asthma exacerbations and decrease the need for oral corticosteroids.*
A. L. L.

Ducharme FM, Chabot G, Polychronakos C, Glorieux F, Mazer B: Safety profile of frequent short courses of oral glucocorticoids in acute pediatric asthma: impact on bone metabolism, bone density, and adrenal function. **Pediatrics** 111:376-383, 2003. ♦♦

Survey Shows High Prevalence of Dust Mite Allergen in U.S. Homes

INDOOR allergens, especially dust mite, are thought to play a role in the rising prevalence of asthma. Data from a U.S. national sample of homes were used to assess the prevalence of dust mite allergen in beds and to identify factors associated with higher concentrations of this allergen.

The analysis included 831 housing units including in the first National Survey of Lead and Allergens in Housing, performed during 1998-99. Measurement of Der f 1 and Der p 1 in dust samples from beds showed a highly skewed distribution. Detectable levels of allergen were found in 84.2% of homes. About one-half of homes had a mite allergen level of at least 2.0 μg/g, the suggested threshold for allergic sensitization. One-fourth of homes had an allergen level of at least 10.0 μg/g, the suggested threshold for triggering asthma. Independent predictors of high mite allergen levels were regions other than the West, high humidity, older home, musty or mildew odor, heat other than gas or electric forced air, lower income, absence of children, and single-family home. The use of impermeable mattress covers and other allergen avoidance measures was not significantly related to allergen levels.

Detectable levels of dust mite allergen are found in bed dust samples in 5 of 6 U.S. homes. Mite allergen concentrations are higher in older homes, those in regions other than the West, and those with high humidity levels.

COMMENT: *This analysis of the first National Survey of Lead and Allergens in Housing shows that dust mite allergens are practically ubiquitous, detectable in 84.2% of all homes studied. Almost half of all homes had 2.0 μg/g of dust, considered to be the threshold for mite allergic sensitization, and a quarter of all the homes had 10.0 μg/g, the level that predisposes to asthma. The independent predictors reported were most convincing for homes with forced-air heating and increased humidity and mustiness. With these data, one wonders if our increasing prevalence of asthma may be attributed, at least partially, to a pesky insect.*
S. M. F.

Arbes SJ Jr, Cohn RD, Yin M, et al: House dust mite allergen in US beds: results from the first National Survey of Lead and Allergens in Housing.
J Allergy Clin Immunol 111:408-414, 2003. ♦♦

Yet More on the Hygiene Hypothesis

IT has been suggested that infections early in life may protect against later development of atopy, possibly by inducing a shift to secretion of Th1 cytokines. Some studies have suggested that infants vaccinated with bacille Calmette-Guérin (BCG) have lower rates of atopy and asthma. Rates of allergic sensitization and atopic disease were compared for Australian children with and without neonatal BCG vaccination. ➤➤

The analysis included children who were born in two districts of Sydney between 1985 and 1994 and whose mothers were born in certain Southeast Asian countries. During the period studied, infants born to mothers from these countries routinely received BCG vaccination in one district but not the other. When the children were 7 to 14 years old, they were assessed for allergic sensitization and allergic diseases by questionnaire, spirometry, airway hyperresponsiveness testing, and allergen and tuberculin skin tests. Blood samples were obtained to measure total serum IgE and to assess in vitro lymphocyte responses to allergens.

The study included 309 children who received BCG vaccination in childhood and 442 who did not. There was no difference in the rate of allergic sensitization between the two groups. However, BCG vaccination was associated with a lower rate of current asthma for children with a family history of rhinitis or eczema: relative risk 0.46 (95% confidence interval 0.22 to 0.95).

The investigators also looked at the relationship between the intensity of delayed-type hypersensitivity to tuberculin and the prevalence of atopy. In the BCG-vaccinated group, 14% of children had reactions of greater than 5 mm to tuberculin skin testing, while 18% had a lymphocyte interferon-γ response to purified protein derivative of *Mycobacterium tuberculosis*. Rates of allergic sensitization or allergic disease were no lower in this subgroup than for vaccinated children without a positive skin test or IFN-γ reaction.

Vaccination with BCG does not affect the overall prevalence of childhood allergic disease. However, BCG may be associated with a reduced rate of current asthma in children with a family history of allergy. Neonatal exposure to BCG may influence clinical airway disease without apparent effects on immediate hypersensitivity. The authors note that their findings were obtained in a population with a low rate of tuberculosis infection but high rate of allergic disease.

COMMENT: *Bacille Calmette-Guérin is a potent Th1 stimulus, but previous studies have reported various results in the development of atopy after BCG administrations. The populations of these studies may have been affected by selection bias. These researchers took advantage of the fact that one community in Sydney, Australia, routinely administered BCG to infants of mothers born overseas while the other did not. There was no effect of BCG on the overall prevalence of atopy. However, in a subgroup of children with family histories of allergy, there was a reduced risk of developing asthma in the BCG-treated infants. In vitro T cell responses did not demonstrate significant differences in allergen-stimulated interleukin (IL)-4, IL-5, or IFN-γ levels between the BCG and non-BCG groups. However, IL-10 responses to dust mite were reduced in the BCG children. This unique study does not confirm the "hygiene hypothesis," but it adds support to the concept that external exposures in infancy do ultimately affect the immune system and can influence the development of allergies, particularly in children from allergic families.*
S. M. F.
Marks GB, Ng K, Zhou J: The effect of neonatal BCG vaccination on atopy and asthma at age 7 to 14 years: an historical cohort study in a community with a very low prevalence of tuberculosis infection and a high prevalence of atopic disease.
J Allergy Clin Immunol 111:541-549, 2003. ♦♦

INCREASES in allergic disease in Western countries have coincided with the cessation of routine vaccination with BCG. In Greenland, routine BCG vaccination was halted in 1990. The effects of BCG vaccination and age at vaccination on atopy risk were assessed.

The study included 1,686 children, aged 8 to 16 years, living in four towns on the northwest coast of Greenland. Most of the children were of Inuit origin. Complete information on BCG vaccination, including age at vaccination, was available for 1,686 children. The presence of atopy was assessed by serum tests of specific IgE against common inhalant allergens.

In logistic regression analyses, the prevalence of atopy was not significantly different for children who did and did not receive BCG vaccination. Age at vaccination had no significant impact on atopy risk.

The results do not support the hypothesis that BCG vaccination reduces atopy risk, regardless of age at vaccination. Lack of selection bias is a strength of the study. However, it cannot exclude effects of BCG vaccination in groups with different genetic backgrounds.

COMMENT: *The hygiene hypothesis is an attractive explanation of the increasing prevalence of allergic disease, but it remains a hypothesis. Animal data have shown than the Th1/Th2 balance may be affected early in life by a variety of measures, including BCG administration. Alas, man is not mouse. This study does not refute the hygiene hypothesis or nullify the possibility that other measures would reduce atopy.*
D. K. L.
Krause TG, Hviid A, Friborg J, et al: BCG vaccination and risk of atopy.
JAMA 289:1012-1015, 2003. ♦♦

Montelukast Add-on Therapy Is Effective for Inadequately Controlled Adult Asthma

ALTHOUGH inhaled corticosteroids (ICS) influence many of the inflammatory pathways involved in asthma, they do not address the cysteinyl leukotriene pathway. This could account for failure to achieve good asthma control in some patients, and suggests that antileukotriene drugs could be a useful alternative to increasing the dosage of ICS. The effects of montelukast add-on therapy were compared with those of a double-dose of ICS in adult asthma patients.

The randomized, controlled trial included 889 adult patients with continued asthma symptoms despite inhaled budesonide, 800 μg/d. After a 1-month run-in period, patients were either started on montelukast 10 mg/d in addition to budesonide 800 μg/d or their inhaled budesonide dose was increased to 1,600 μg/d. Measures of asthma control were assessed after 12 weeks' treatment. ➤➤

Both strategies brought significant improvement in disease control. The increase in morning peak expiratory flow (PEF) during the last 10 weeks of treatment was 33.5 L/min with montelukast plus budesonide and 30.1 L/min with double-dose budesonide. However, during the first 3 days, patients taking montelukast add-on therapy had a significantly greater increase in morning PEF: 20.1 vs 9.6 L/min.

Changes in other measures were similar between groups, including β-agonist use, daytime symptom score, nighttime awakenings, exacerbations, asthma-free days, peripheral eosinophil counts, and disease-specific quality of life. Both treatments were well tolerated.

For adult patients whose asthma is inadequately controlled by inhaled budesonide 800 µg/d, add-on therapy with montelukast provides an effective alternative to double-dose budesonide. The two treatments are similarly effective, although onset of action may be faster with montelukast.

COMMENT: *Although several studies have demonstrated additive effects of montelukast with ICS, none have compared this effect with higher-dose ICS. This study represents a 16-week randomized controlled trial in 889 adults with inadequately controlled asthma on inhaled budesonide 800 µg/d. Patients received montelukast 10 mg/d plus budesonide 800 µg/d or inhaled budesonide 1,600 µg/d. Both groups had similar improvements in primary and secondary endpoints. The major weaknesses of this study are its short duration and lack of a placebo group. Further long-term studies will be required to detect possible differences in exacerbation rates. It must also be remembered that leukotriene receptor antagonists might be less effective in patients with moderate or severe asthma.*
E. J. B.

Price DB, Hernandez D, Magyar P, et al, for the Clinical Outcomes with Montelukast as a Partner Agent to Corticosteroid Therapy (COMPACT) International Study Group: Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma.
Thorax 58:211-216, 2003. ♦♦

Study Shows Lasting Effectiveness of SLIT

SUBCUTANEOUS immunotherapy is a proven treatment for patients with respiratory allergies, showing continued efficacy long after the end of treatment. Sublingual immunotherapy (SLIT) is a popular alternative, especially in Europe, and has demonstrated short-term clinical efficacy. The long-term outcomes of SLIT were evaluated in a prospective, controlled trial.

The study included two matched groups of children, mean age 8.5 years, with allergic rhinitis or asthma caused by dust mites. Thirty-five children received 4 to 5 years of SLIT, using a standardized extract of *Dermatophagoides pteronyssinus* as well as *Dermatophagoides farinae*, taken as aqueous drops each morning. The 25 children in the control group received drug treatment only. Symptoms, peak expiratory flow rates, and other outcomes were evaluated at baseline, at the end of SLIT, and 4 to 5 years afterward.

The prevalence of asthma was significantly reduced in patients receiving SLIT, both at the end of treatment and at long-term follow-up. Children in the SLIT group also used significantly less medication for asthma at both times. Peak expiratory flow measurements also favored SLIT.

The results of this open trial suggest that SLIT has long-lasting benefits in children with asthma caused by dust mite allergy. Asthma symptoms are still reduced 4 to 5 years after the end of SLIT, compared to children treated with antiasthma medications only.

COMMENT: *Long considered by the mainstream of our specialty to be a "fringe" practice, SLIT has been legitimized in recent years by multiple controlled trials and is widely practiced in Europe. The administration of high-dose SLIT is not associated with a risk of systemic reactions, and therefore it has a safety advantage over subcutaneous immunotherapy. This prospective study from Italy suggests that SLIT, like subcutaneous immunotherapy, results in continued benefit for at least several years after it is discontinued.*
S. A. T.

Di Rienzo V, Marcucci F, Puccinelli P, et al: Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study.
Clin Exp Allergy 33:206-201, 2003. ♦♦

Men With Rhinitis Have Higher Blood Pressure

RESPIRATORY function abnormalities have been linked to cardiovascular disease. Through its association with snoring and obstructive sleep apnea, rhinitis might be associated with hypertension. Population-based data were used to assess the relationship between rhinitis and arterial blood pressure.

The analysis included 330 adult subjects from the follow-up phase of the European Community Respiratory Health Survey. A questionnaire was used to assess rhinitis and cardiovascular risk factors and disease. Blood pressure measurements were obtained, along with spirometric measurements of forced vital capacity and FEV_1.

Twenty-eight percent of men and 44% of women in the sample had rhinitis. Mean systolic blood pressure was 130.6 mm Hg in men with rhinitis compared with 123.5 mm Hg in those without rhinitis. A similar relationship was noted on analysis excluding men with asthma and after adjustment for treatment. Among the men with rhinitis, systolic blood pressure was higher for those with perennial vs seasonal symptoms. Men with rhinitis also had a higher prevalence of hypertension, 35.7% vs 15.6%. Rhinitis was unrelated to blood pressure in women.

Rhinitis is strongly associated with increased systolic blood pressure and hypertension in men. Blood pressures are higher in men with perennial rhinitis, suggesting a "dose-response" relationship. The mechanism of the association is unknown; however, if it is medi- ➤➤

ated by obstructive sleep apnea, that might account for the lack of association between rhinitis and blood pressure in women.

COMMENT: *Perhaps too often, subspecialists can be too focused in their office encounters. Something as simple as vital signs assessment for a patient being evaluated or followed for allergic rhinitis can be ignored as irrelevant to the specific medical problem being treated in the allergist's office. This French study involved 330 young adults (ages 28 to 56) participating in the European Community Respiratory Health Survey. The results are provocative in that they showed a higher systolic blood pressure in men with rhinitis than in those without. Further, there was an increased risk of hypertension (OR 2.6) in male rhinitis patients. Finally, the risk increased according to the duration of the rhinitis (perennial vs seasonal vs none). These data emphasize the need for allergists to continue to provide comprehensive medical care (which includes regular vital signs assessment) even in patients with "simple" medical problems.*
G. D. M.
Kony S, Zureik M, Neukirch C, et al: Rhinitis is associated with increased systolic blood pressure in men: a population-based study.
Am J Respir Crit Care Med 167:538-543, 2003. ♦♦

Skin Prick Reactivity Is Closely Linked to Bronchial Hyperresponsivness in Asthma

IN patients with asthma, skin prick testing (SPT) is performed to assess the presence of atopy to inhaled allergens, while bronchial challenge tests are done to evaluate bronchial hyperresponsiveness (BHR). The nature of the relationship between atopy and BHR is unclear. Associations between the results of SPT and BHR tests were evaluated in patients with asthma.

The retrospective study included 332 asthma patients: 194 women and 138 men, mean age 37 years. All underwent SPT using a panel of eight common aeroallergens. They also underwent bronchial challenge testing with methacholine and adenosine monophosphate, along with spirometry. Relationships among the degree of SPT reactivity, BHR, and spirometry were assessed.

Among patients with SPT results demonstrating atopy, the provocative dose of methacholine causing a 20% reduction in FEV_1 was significantly lower in those with BHR to methacholine but not AMP. The geometric mean difference between these groups was 2.3-fold (95% confidence interval 1.4 to 4.0). In addition, patients with a higher number of skin prick positive (SPP) responses had lower methacholine PD_{20} values: 69.9 μg for those with 0 or 1 SPP responses, 47.8 μg for those with 2 to 4 SPP responses, and 35.6 μg for those with 5 to 8 SPP responses. Thus there was a 2-fold difference in methacholine responsiveness between the groups with the lowest and highest skin prick reactivity.

Analysis restricted to perennial allergens yielded similar findings. The results of SPT and spirometry were unrelated.

In patients with asthma, the degree of response to SPT using common aeroallergens is significantly related to methacholine BHR. This association is unaffected by the spirometric findings, inhaled corticosteroid therapy, or reaction to perennial or seasonal allergens. Bronchial hyperresponsiveness and atopy appear to play very closely related roles in the development of asthma.

COMMENT: *This study was performed to clarify the relationship between the degree of BHR and SPT positivity, and to explore differences with direct and indirect bronchial challenge. Results revealed a compelling relationship between SPT positivity to aeroallergens and BHR to methacholine. No relationship was seen with indirect bronchial challenge. This study adds to the evidence that asthma is a heterogeneous disorder. One wonders what differences between direct and indirect bronchial challenge one would see in SPT-negative patients.*
E. J. B.
Fowler SJ, Lipworth BJ: Relationship of skin-prick reactivity to aeroallergens and hyperresponsiveness to challenges with methacholine and adenosine monophosphate. **Allergy** 58:46-52, 2003. ♦♦

Inhaled Corticosteroids Don't Increase Hip Fracture Risk in Older Women

INHALED corticosteroids are assumed to have fewer adverse effects on bone metabolism than systemic corticosteroids. However, the relationship between inhaled corticosteroid use and clinical fracture rates is uncertain. The association between hip fracture risk and inhaled corticosteroid use among elderly women was assessed.

Canadian health care data were used to identify four groups of elderly women using various drugs: inhaled corticosteroids, approximately 25,000 women; systemic corticosteroids, 28,000 women; estrogen, 28,000 women; and proton pump inhibitors, 35,000 women. Rates of hospitalization for hip fracture were compared among groups.

During the 7-year observation period, 931 hip fractures occurred. From lowest to highest, the incidence of hip fracture was 3.1/1,000 person years in women using estrogen, 9.6/1,000 in those using inhaled corticosteroids, 10.7/1,000 in those using proton pump inhibitors, and 12.1/1,000 in those using systemic corticosteroids. Compared to the proton pump inhibitor group, hip fracture rate was significantly reduced in the estrogen group, significantly elevated in the systemic corticosteroid group, and not significantly different in the inhaled corticosteroid group.

Inhaled corticosteroid use does not appear to increase the risk of hip fracture among elderly women. When indicated, inhaled corticosteroids should be included among the therapeutic options for older women with respiratory diseases. The inhaled corticosteroid group in this study included patients with chronic obstructive pulmonary disease. ➤➤

COMMENT: *Postmenopausal women are at high risk of hip fractures from systemic corticosteroid use. The risks related to inhaled corticosteroids are largely unknown. This retrospective cohort study linked health care data bases for 800,000 women (66 years or older) in Ontario, Canada. Analysis of the results indicated that inhaled corticosteroids were not associated with an increased risk of hip fracture.*
E. J. B.
Lau E, Mamdani M, Tu K: Inhaled or systemic corticosteroids and the risk of hospitalization for hip fracture among elderly women.
Am J Med 114:142-145, 2003. ♦♦

Levalbuterol vs Racemic Albuterol for Hospitalized Patients

RACEMIC albuterol is made up of an (R)-isomer and an (S)-isomer. (R)-albuterol, or levalbuterol, is the active bronchodilator. In contrast, (S)-albuterol actually promotes smooth muscle contraction, resulting in increased bronchial reactivity. Using levalbuterol rather than racemic albuterol prevents these potentially harmful effects. The clinical effectiveness and costs of using levalbuterol in hospitalized patients were reviewed.

The retrospective study included patients treated in one regional hospital for chronic obstructive pulmonary disease (COPD) or asthma during nonconsecutive 6-month periods in 1998 and 1999. The 125 patients treated in 1998 received nebulized racemic albuterol, while the 109 patients treated in 1999 received levalbuterol. Outcomes were compared between groups, including number of nebulizer treatments, symptomatic improvement, and length of hospital stay.

The discharge diagnosis was COPD in 72% of patients receiving racemic albuterol and 82% receiving levalbuterol. Mean number of nebulizer treatments was 31 in the racemic albuterol group vs 19 in the levalbuterol group. Among asthma patients, the difference was even greater: 30 vs 14, respectively. Costs of nebulizer therapy were also lower with levalbuterol. Mean length of hospital stay was 5.6 days in patients treated with racemic albuterol vs 4.7 days in those treated with levalbuterol. Total costs were lower in the levalbuterol group, although the difference was nonsignificant. On regression analysis, levalbuterol was associated with nearly a 1-day reduction in hospital stay, a cost savings of $550, and a 67% reduction in the rate of hospital readmission.

Levalbuterol offers several advantages over racemic albuterol in the treatment of hospitalized patients with COPD or asthma. Levalbuterol is associated with lower medication use, shorter length of stay, and longer duration of therapeutic benefit. The study confirms the benefits of levalbuterol in a "real-world" setting.

COMMENT: *Most medications are now in the form of the active metabolite or single isomer of the drug. Here we see further evidence why this is the case. Levalbuterol is shown to help patients do better while in the hospital and to leave quicker without return, compared with patients on racemic albuterol. Further evidence is provided to turn to this medication in asthma or COPD exacerbations in order to provide better care and lower hospitalization costs.*
A. L. L.
Truitt T, Witko J, Halpern M: Levalbuterol compared to racemic albuterol: efficacy and outcomes in patients hospitalized with COPD or asthma.
Chest 123:128-135, 2003. ♦♦

In Utero Smoking Exposure and Early-Onset Asthma Linked to Reduced Lung Function

PREVIOUS studies have reported reductions in lung function in children with prenatal exposure to maternal smoking and asthma, particularly early-onset asthma. Data from the Children's Health Study were used to assess the effects of in utero exposure to maternal smoking on lung function in children with and without asthma.

The analysis included information on 5,933 schoolchildren, including longitudinal data on history of respiratory illness, exposure to environmental tobacco smoke, and maternal smoking. At baseline, 8.7% of children had received a diagnosis of asthma at age 5 years or younger and 8.6% after age 5.

Both in utero exposure to maternal smoking and early-onset asthma were associated with significant reductions in lung function. Even in children without asthma, in utero exposure to maternal smoking was associated with reductions in FEF_{25-75}, the FEV_1/FVC ratio, and the FEF_{25-75}/FVC ratio. In both boys and girls, the effects of in utero exposure to maternal smoking were greater for those with early-onset asthma.
In vitro exposure plus early-onset asthma in boys was associated with deficits of 13.6% in FEV_1, 9.1% in FEV_1/FVC, 29.7% in FEF_{25-75}, and 25.9% in FEF_{25-75}/FVC. In girls, the same combination was associated with reductions of 9.3% in FEV_1/FVC, 26.6% in FEF_{25-75}, and 29.9% in FEF_{25-75}/FVC. These deficits persisted into adolescence. On its own, environmental tobacco smoke did not seem to have major adverse effects.

In utero exposure to maternal smoking and early-onset asthma are associated with substantial and lasting deficits in pulmonary function in children. The effects of maternal smoking appear particularly damaging in children with early-onset asthma. Especially in terms of airflow measures, the findings cannot be explained by exposure to environmental tobacco smoke after birth.

COMMENT: *This study reaffirms the adverse effects of smoking by pregnant women on lung function in all the children they bear. The authors studied approximately 6,000 subjects from the Children's Health Study. They showed that the largest effect on FEV_1, FEV_1/FVC, and FEF_{25-75} occurred in in utero exposed children who subsequently developed asthma, particularly if early-onset. Of interest, in this study extrauterine environmental tobacco exposure had minimal effects on airway function. These data reaffirm the high risk to infants' lung function of mother smoking during pregnancy.* ➤➤

G. D. M.
Gilliland FD, Berhane K, Li Y-F, et al: Effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function.
Am J Respir Crit Care Med 167:917-924, 2003. ♦♦

Cat Ownership Increases Risk of Cat Allergy

THE presence of cats and dogs in the home is generally thought to increase the risk of sensitization to pet allergens. However, some cross-sectional studies have questioned this association. Data from the prospective, population-based Copenhagen Allergy Study were used to assess the association between pet allergies and the presence of pets in the home.

Seven hundred thirty-four adults living in Copenhagen responded to a questionnaire on respiratory symptoms and underwent serum IgE antibody measurement. The subjects were studied on two occasions, in 1990 and 1998. The participation rate was 69%.

Currently having a cat in the home was strongly associated with sensitization to cat, odds ratio 8.43. No such association was noted with currently keeping a dog; the rate of cat sensitization actually tended to be lower among dog owners. Previously having a cat at home was significantly related to allergic rhinitis to animals overall, while currently having a cat was associated with allergic asthma to animals.

Keeping a cat at home is associated with an increased risk of sensitization to cat allergen. In contrast, keeping a dog does not increase the risk of sensitization to dog. The relationship between pet cats and allergic asthma to animals suggests an association between exposure to cat allergen and risk of allergic respiratory disease.

COMMENT: *There have been conflicting results related to the impact of cat in the home and the risk of developing sensitization to cat. Some studies have shown a positive association, while others have not. In fact, some studies have shown a negative association. In this prospective, population-based analysis of 734 subjects (15 to 69 years old), currently having a cat in the home was positively associated with the incidence of sensitization to cat. In contrast, this was not true for dog in the home. The authors correctly emphasize the need for additional large-scale prospective studies on this issue.*
E. J. B.
Linneberg A, Nielsen NH, Madsen F, et al: Pets in the home and the development of pet allergy in adulthood. The Copenhagen Allergy Study.
Allergy 58:21-26, 2003. ♦♦

MDI Plus Spacer Has Advantages in ED Treatment of Children Aged 2 or Younger

STUDIES in older children and adults with asthma have found that metered-dose inhalers (MDIs) provide a fast and cost-effective means of delivering aerosolized bronchodilators. Although MDIs are difficult for younger children to use, the use of a spacer allows them to receive medications while breathing normally via a face mask or mouthpiece. The use of an MDI with spacer was compared with a nebulizer for delivery of albuterol in emergency department treatment of infants and toddlers with wheezing.

The randomized, controlled trial included 168 children, aged 2 to 24 months, treated for wheezing in a New York City pediatric emergency department. Children assigned to the nebulizer group first received a placebo via MDI with spacer, followed by nebulized albuterol. Those assigned to the MDI group initially received albuterol via MDI with spacer, followed by nebulized isotonic sodium chloride solution. The children's responses were monitored every 20 minutes in blinded fashion.

The children's mean age was 11.7 years; most were Latino or African-American boys. Mean initial Pulmonary Index was significantly higher in children assigned to the nebulizer group: 7.6 vs 6.6. After controlling for this baseline difference, the hospitalization rate was 5% for children in the MDI plus spacer group vs 20% for those in the nebulizer group. Mean number of treatments or requirement for steroids was not significantly different between groups. There was a significant interaction between treatment group and baseline Pulmonary Index--most of the reduction in hospitalization rate among the MDI group occurred among children with more severe asthma exacerbations.

In the ED treatment of wheezing in infants and younger children, albuterol delivery via MDI with spacer appears at least as effective as albuterol via nebulizer. For children with more severe exacerbations, the use of MDI with spacer appears to reduce the rate of hospitalization. After controlling for baseline differences in Pulmonary Index, the risk of admission is three times higher for children assigned to nebulized albuterol.

COMMENT: *As with similar studies done in older children or adults, this study in very young children demonstrated that delivery of albuterol aerosols via MDI plus a spacer was as efficacious as delivery via nebulizer. Interestingly, in this study the MDI plus spacer treatment group also received 3 mL of nebulized isotonic saline (after the albuterol administered via MDI). Could this type of additional treatment improve the delivery of MDI albuterol in the younger age group?*
J. A. A.
Delgado A, Chou KJ, Silver EJ, Crain EF: Nebulizers vs metered-dose inhalers with spacers for bronchodilator therapy to treat wheezing in children aged 2 to 24 months in a pediatric emergency department.
Arch Pediatr Adolesc Med 157:76-80, 2003. ♦♦

Montelukast Is Effective for Springtime Allergic Rhinitis

CYSTEINYL leukotrienes contribute to the symptoms of asthma, as evidenced by the clinical effectiveness of antileukotriene therapy with montelukast. This randomized, controlled trial assessed the use of montelukast therapy for springtime treatment of patients with seasonal allergic rhinitis. ➤➤

The multicenter study included 1,214 patients with spring allergic rhinitis. All patients had a positive skin test to a springtime allergen and a documented history of daytime nasal symptoms. After 3 to 5 days of placebo run-in therapy, patients received 2 weeks of treatment with montelukast 10 mg/d, 521 patients; loratadine 10 mg/d, 171 patients; or placebo, 521 patients. Daily nasal symptom scores were compared among groups.

The study completion rate was over 95%. Montelukast offered significant reduction in daytime nasal symptoms, compared with placebo. Patient and physician global evaluations also supported the effectiveness of montelukast. Loratadine also improved most nasal symptoms compared with placebo, except for nighttime symptoms.

Comparison of the two active treatments favored montelukast for eosinophil counts and loratadine for daytime eye symptoms and for eye and nasal symptoms at the end of the day. Montelukast and loratadine were both well tolerated.

Montelukast is a clinically effective treatment for springtime seasonal allergic rhinitis. Benefits of this antileukotriene medication include reductions in nighttime symptoms and improvement in quality of life scores.

COMMENT: *This large clinical trial, along with others, has demonstrated the clinical efficacy and safety of montelukast in allergic rhinitis. The magnitude of the response appears similar to that of loratadine. Further comparative studies with more efficacious antihistamines as well as intranasal corticosteroids are needed to determine the positioning of montelukast in the treatment of allergic rhinitis. (Please see the article by Nathan cited in this issue's "Reviews of Note.")*
A. M.

van Adelsburg J, Philip G, LaForce CF, et al, and the Montelukast Spring Rhinitis Investigator Group: Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis.
Ann Allergy Asthma Immunol 90:214-222, 2003. ♦♦

Can Sinus CT and Inflammatory Markers Differentiate VCD from Asthma?

PATIENTS with vocal cord dysfunction (VCD) have inappropriate closure of the vocal cords, mainly on inspiration. This condition is commonly mistaken for asthma, sometimes leading to high doses of antiasthma medications. This study evaluated the use of sinus CT scan and inflammatory markers to differentiate between VCD and asthma.

Four groups of subjects were studied: 13 patients with VCD, diagnosed by laryngoscopy; 77 patients seen in the emergency department for acute asthma; 31 patients with nonacute asthma; and 65 nonasthmatic controls. Each subject underwent sinus CT scanning, with scoring for extent of sinus disease. The three groups were also compared for inflammatory markers, including exhaled nitric oxide, circulating eosinophil count, and total serum IgE.

The sinus CT scans showed "extensive" sinus disease in none of the patients with VCD, compared to 31% of patients with acute asthma, 17% of those with nonacute asthma, and 3.5% of nonasthmatic controls. All four groups had higher and comparable rates of less-severe sinus abnormalities. Exhaled nitric oxide and other inflammatory markers were not significantly different between the VCD group and the nonasthmatic controls. Five patients thought to have acute asthma in the ED were found to have VCD on laryngoscopic examination. These patients lacked significant findings of inflammation on sinus CT; they had low serum IgE levels and normal circulating eosinophils.

In the evaluation of patients with intermittent or reversible airway obstruction, VCD may be differentiated from asthma by the lack of significant sinus inflammation on CT scan and by the absence of elevated inflammatory markers. In contrast, about one-third of patients with acute asthma seen in the ED have significant sinus abnormalities. Clinical symptoms are not a good predictor of the presence or absence of sinus disease.

COMMENT: *Recognizing VCD and distinguishing this condition from asthma is a major clinical challenge. Unfortunately, the tests investigated in this paper are not sufficiently sensitive or specific to identify asthma, and coincident VCD and asthma cannot be recognized by tests for asthma. Direct visualization of the vocal cords during symptomatic episodes is the only definitive method to diagnose VCD.*
D. K. L.

Peters EJ, Hatley TK, Grater SE, et al: Sinus computed tomography scan and markers of inflammation in vocal cord dysfunction and asthma.
Ann Allergy Asthma Immunol 90:316-322, 2003. ♦♦

Peanut Allergy Transferred to Liver Transplant Recipient

PREVIOUS reports have described persistent transfer of allergen-specific IgE-mediated hypersensitivity to allogeneic bone marrow recipients. This case report describes transfer of peanut allergy to a liver transplant recipient.

The donor, who had a history of atopic dermatitis, asthma, and food allergies, died of anaphylaxis after peanut ingestion. His liver was transplanted to a man with chronic hepatitis B, cirrhosis, and hepatoma. After discharge, the recipient experienced anaphylaxis after eating cashews, to which he had never previously reacted. Follow-up skin prick testing confirmed nut allergy. Patients who had received the donors kidneys and pancreas had no evidence of nut allergy. The liver recipient had no detectable donor leukocytes on molecular HLA typing studies.

This is only the second reported case of allergy transfer after solid organ transplantation. The mechanism of transfer is unclear; passive transfer of donor IgE is a possibility. ➤➤

COMMENT: *This interesting case history describes a 60-year-old man who suffered anaphylaxis to cashew nut 25 days after receiving a liver allograft from a 15-year-old atopic boy who died of peanut anaphylaxis. Recipients of other solid organs from the same donor had no evidence of allergic symptoms after peanut or cashew ingestions. Molecular HLA typing failed to detect any donor-origin leukocytes in the recipient, excluding peripheral microchimerism. The mechanism of transfer remains to be elucidated. Fascinating case!*
E. J. B.
Phan TG, Strasser SI, Koorey D, et al: Passive transfer of nut allergy after liver transplantation.
Arch Intern Med 163:237-239, 2003. ♦♦

Sibling Effects on Atopy Risk in Children of Asthmatic Parents

THERE is evidence for sibling effects on the risk of atopic disease. However, few studies have assessed the potential sibling effect in families at high risk of atopy. This study evaluated the existence of a sibling effect on atopy among children with a family history of asthma.

The study included 541 first-degree offspring of 200 probands with asthma, seen at a Dutch regional asthma center. Serum total IgE, specific IgE, and skin test reactions were assessed as markers of atopy and bronchial hyperresponsiveness (BHR) to methacholine as a marker of asthma.

The oldest siblings had the highest rates of positive skin tests, 55%; specific IgE to aeroallergens, 46%; and BHR, 50%. On multivariate analysis, having older siblings was inversely related to risk of atopy, based on number of positive skin tests. Larger families had a lower prevalence of specific IgE to aeroallergens. With adjustment for age, sex, smoking, and eosinophil count, birth order and family size had no significant effect on BHR.

For families in which a parent has asthma, rates of skin test positivity are lower for children with older siblings. In larger families, the children are less likely to have specific IgE to common aeroallergens, regardless of birth order. No sibling effect is noted on total IgE or methacholine BHR. The study also finds an association between passive smoking during the first 3 years of like and increased specific IgE levels in these high-risk families.

COMMENT: *Sibling effects on atopy and asthma have been repeatedly observed in general population studies, and include a protective effect of having larger families, especially in the youngest children of large families. The effect has been less clear within atopic (high-risk) families. This study evaluated 200 Dutch families with at least one asthmatic parent. There was a sibling effect for the presence of specific IgE but not for total IgE levels or BHR. (However, the study was not powered to detect a protective effect on BHR.) The authors point out that the basis for this effect has not yet been proven, though the leading hypothesis argues the existence of a protective effect of an increased number of childhood infections in larger families.*
S. A. T.
Koppelman GH, Jansen DF, Schouten JP, et al: Sibling effect on atopy in children of parents with asthma.
Clin Exp allergy 33:170-175, 2003. ♦♦

Fungi in Indoor Air vs Dust Samples Aren't Closely Related

THE relationship between exposure to fungi and asthma risk remains unclear. One reason is the differing measures of fungal exposures used: some studies have relied on dampness or visible fungi while others have used culture of air or dust samples. The association between dustborne and airborne fungal levels were assessed, including factors potentially influencing this relationship.

The analysis included dust samples from 397 homes and air samples from 496 homes with newborn infants in the Boston area. A Burkard culture plate sampler was used to obtain indoor and outdoor air samples, after which a dust samples were obtained from the floor around the infant's bed. Fungal types and concentrations were measured in the three types of samples.

Yeasts were more frequently found in dust samples than in air samples. In both indoor and outdoor air samples, the most frequently detected taxa were nonsporulating fungi, *Penicillum*, and *Cladosporidium*. The same taxa were also commonly recovered from dust samples. Mean fungal concentrations were 580 cfu/m^3 in indoor air, 986 cfu/m^3 in outdoor air, and 200,473 cfu/g in dust.

There was a significant correlation between total culturable fungi in indoor and outdoor air, but not between indoor air and dust. Certain indoor-air fungi were significantly associated with fungi in outdoor air and dust, eg, *Cladosporidium*. Airborne concentrations of specific fungi were strongly affected by sampling seasons. Type of housing and relative humidity were significant predictors of fungal levels.

Levels of culturable fungi in dust and indoor air samples are not strongly related to each other. The findings of dust vs air sampling may reflect differing types of fungal exposure. Housing-related variables may also affect the results. For complete evaluation of fungal exposure, it may be necessary to collect both air and dust samples.

COMMENT: *Dust sampling in homes is often a surrogate measure for respiratory exposure to fungi. These investigators collected sequential duplicate air samples in bedrooms in 496 homes in the Boston area from 1994 to 1996. They found little association between culturable fungi in indoor air and dust. Other housing characteristics had a negative effect on fungi in the dust, including the study of apartments (as opposed to homes), absence of carpeting, and absence of a dog in the home. Of interest, resident reports of mold or mildew and water damage were not significantly associated with higher levels of fungi in the air or in the dust.*
E. J. B.
*Chew GL, Rogers C, Burge HA, et al: Dustborne and airborne fungal propagules represent a different spectrum of fungi with differing relations to home characteristics.***Allergy** 58:13-20, 2003. ♦♦

REVIEWS OF NOTE

COMMENT: *This beautifully written and illustrated review is an explanation of the modern understanding of the "miracle" of immunologic diversity. It walks us through antigen recognition, clonal selection, differentiation from "self," and rational therapeutic interventions in the immune response. It is short and sweet, and very intelligible.*
R. J. M.
Schwartz RS: Shattuck Lecture--diversity of the immune repertoire and immunoregulation.
N Engl J Med 348:1017-1026.

COMMENT: *This article is a thorough review of the "allergic march" from atopic dermatitis to bronchial asthma. A panel of experts present reviews of epidemiologic studies, association studies between asthma and atopic dermatitis, environmental studies, and genetic studies. They suggest we should soon look for guidelines for the treatment of atopic dermatitis (GREAT!). Atopic dermatitis is often unappreciated as the first step in the development of other atopic diseases such as asthma. This article provides an understanding of the process and the latest treatment options.*
A. L. L.
Eichenfield LF, Hanifin JM, Beck L, et al: Atopic dermatitis and asthma: parallels in the evolution of treatment. **Pediatrics** 111:608-616, 2003.

COMMENT: *In discussions of systemic side-effects of corticosteroid therapies, the hypothalamic-pituitary-adrenal (HPA) axis is frequently mentioned as a major concern. Yet, from personal surveys I have taken, very few clinicians have ever encountered a case of clinical adrenal insufficiency due to exogenous steroid use. This excellent review points out that* relative *adrenal insufficiency and* functional *adrenal insufficiency may occur in acutely ill patients even with "normal" plasma cortisol levels. They recommend a low threshold for testing HPA function, and for prescription of physiologic replacement doses, in acutely ill patients.*
R. J. M.
Cooper MS, Stewart PM: Corticosteroid insufficiency in acutely ill patients. **N Engl J Med** 348:727-734, 2003.

COMMENT: Dr. Nathan summarizes the current medical literature related to rhinitis and leukotriene modifier therapy. He points out some of the inconsistent study results, partially related to the inherent variability in studies using nasal symptom scores as the primary response variable. Clinicians and their patients will likely determine the role of leukotriene modifiers in the management of allergic rhinitis. Additional studies, particularly including quality of life data, would be helpful.
D. K. L.
Nathan RA: Pharmacotherapy for allergic rhinitis: a critical review of leukotriene receptor antagonists compared with other treatments.
Ann Allergy Asthma Immunol 90:182-191, 2003.

COMMENT: *A variety of respiratory syndromes are common in athletes, including asthma, vocal cord dysfunction and postexercise cough. This interesting review focuses on the airway cell changes that occur in endurance athletes, regardless of symptoms or lung function. The authors describe an increase in airway inflammatory cells, perhaps stimulated by a hyperventilation-induced increase in airway osmolarity. A hypothesis is proposed by which hyperventilation induces adhesion molecule shedding and a resultant protective effect on the airway despite the presence of inflammatory cells. If proven, this phenomenon may have implications regarding exercise or hyperventilation as a chronic therapy for some respiratory diseases.*
S. A. T.
Bonsignore MR, Morici G, Vignola AM, et al: Increased airway inflammatory cells in endurance athletes: what do they mean? **Clin Exp Allergy** 23:14-21, 2003.

COMMENT: *This review provides a concise summary of the current understanding of the pathophysiology of dust mite allergy. The authors also point out the need for more animal models of allergen-induced asthma.*
S. A. T.
Sharma S, Lackie PM, Holgate ST: Uneasy breather: the implications of dust mite allergens.
Clin Exp Allergy 33:163-165, 2003.

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