# AllergyWatch®

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

A Publication of The American College of Allergy, Asthma & Immunology

Volume 4, Number 2 March-April 2002


## "Is My Baby Getting Too Many Vaccines?" How to Answer Worried Parents

DURING the twentieth century, the number of vaccines routinely given to children increased from one (smallpox) to eleven--some children receive as many as twenty injections by age 2. These vaccinations have greatly reduced the occurrence of many devastating diseases, to the point where most young parents have never seen the diseases the vaccines prevent. Some parents express concern that their baby's immune system is not mature enough to handle vaccines, or that the vaccinations will overwhelm or "use up" the immune system. This article reviews current knowledge of infants' immune system and its response to vaccinations.

Infants can respond to foreign antigens even before they are born--they have their own B and T cells by 14 weeks' gestation. At birth, they have passively acquired immunity by means of maternal immunoglobulins as well as the full range of active immune responses. Infants' B-cell responses are reduced compared with those of older children or adults, but they respond well to antigens requiring T-cell help.

Newborns display an excellent protective response to vaccines within hours after birth, and can even generate responses to multiple vaccines given at the same time. Live viral or bacterial vaccines may lead to disseminated infection in severely immunocompromised children. However, most children today receive no live viral vaccines until age 12 to 15 months. In addition, many children with immunodeficiencies respond well to live viral vaccines, and this is reflected in current recommendations.

Parents may fear that children are more likely to have an adverse reaction or inadequate response if vaccinated during an acute illness. However, studies have shown that the presence of mild or moderate illness has no effect on the response to vaccination. Parents who voice the concern that vaccination will overwhelm the infant's immune system may be reassured that infants can respond to very large numbers of antigens and that, with modern vaccines, children are actually exposed to far fewer antigens than ➤➤

## CONTENTS




The American College of Allergy, Asthma & Immunology expresses its appreciation to Aventis Pharmaceuticals Inc.for its unrestricted grant in support of the publication of *AllergyWatch*®.

*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

"*AllergyWatch®*" is an official publication and a registered trademark of The American College of Allergy, Asthma & Immunology and is published six times per year in one volume. Subscrition rates: U.S., Individual $90.00 Outside the U.S.: $120.00, Residents, Fellows, Students within the U.S.: $65.00, outside the U.S., add $18.00, bulk subscription pricing available upon request of the publisher. Send subscription inquiries to *AllergyWatch®*,85 West Algonquin Road, Suite 550, Arlington Heights, IL, 60005. Address editorial enquiries to: *AllergyWatch®*, c/o Emil J. Bardana, M.D., Editor, The Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, PV 320, Portland, Oregon 97201-3098. Telephone (503) 494-8531, Fax (503) 494-4323 or via email to bardanae@ohsu.edu.  ISSN 1521-2440.

in the past. Worried parents may also be told that the response to multiple vaccines given at the same time is similar to that of individual vaccinations.

The information presented in this review can help to alleviate parents' concerns over adverse effects of vaccination on infants. Recommended vaccinations do not overwhelm or weaken the infant's immune system. Parents may be reassured that babies can mount an effective immune response not only to multiple vaccines, but also to challenges in the environment.

**COMMENT:** *As physicians, we all know that the immunization of infants to prevent serious infections is very important. However, there is still some natural concern by parents for their infant's welfare when faced with the "baby shots," especially as the number necessary has increased in recent years. This is an excellent article to address this common concern of parents. As a grandfather, I can say it will help answer my family's concerns!*
*J. A. A.*
*Offit PA, Quarles J, Gerber MA, et al: Addressing parents' concerns: do multiple vaccines overwhelm or weaken the infant's immune system?*
**Pediatrics** 109:124-129, 2002. ♦♦

## Parents Are Slow in Drawing Up Epinephrine Doses, Study Finds

FOR infants at risk of anaphylaxis, the physician may prescribe the 0.15 mg EpiPen Jr, which is user-friendly but expensive and carries a risk of overdosage. Alternatively, parents may be given an ampule of epinephrine with a sterile syringe and needle and instructions for administration. The latter technique raises concerns about delays in administration and improper dosing. This study assessed parents' accuracy with the ampule/syringe/needle technique, compared with physicians and nurses.

Eighteen consecutive parents of children with a history of anaphylaxis were timed while drawing up 0.09 mL of epinephrine from an ampule. The content of each epinephrine dose was measured by high-performance liquid chromatography with ultraviolet detection. The parents' performance was compared with that of 18 general duty nurses, 18 emergency department (ED) nurses, and 18 residents.

Mean time to draw up the dose was 142 seconds for parents, compared with 52 seconds for residents, 40 seconds for general duty nurses, and 29 seconds for ED nurses. The mean content of the epinephrine doses was not significantly different among groups. However, the epinephrine content of the parents' doses varied by nearly 40-fold. The ED nurses had the least variation: only 2-fold. When asked to comment, the parents expressed concern about carrying out the technique in a real emergency.

The results question parents' ability to draw up an emergency dose of epinephrine rapidly and accurately. In this study, even the fastest parent was slower than nearly all of the health professionals tested. The ampule/syringe/needle technique appears impractical for use by parents of infants at risk of anaphylaxis.

**COMMENT:** *Once again, Dr. Simons has strengthened the case for low-dose epinephrine autoinjectors for the treatment of infants and toddlers with anaphylaxis. It was of interest that parents--even without the pressure of treating an episode of anaphylaxis in their child--took almost 2.5´ minutes to prepare and administer the injection. On comparison of mean times, parents took more than twice as long as physicians, who took almost twice as long as ED nurses. The data on dose accuracy were also revealing: the range was 40-fold for parents and 7- to 8-fold for physicians but only 2-fold for ED nurses. Clearly, it is suboptimal to use vials of epinephrine for self-administration* ➤➤

*(or child administration) in life-threatening anaphylaxis. When will we have low-dose autoinjectors available?*
*S. M. F.*
*Simons FER, Chan ES, Gu X, Simons KJ: Epinephrine for the out-of-hospital (first-aid) treatment of anaphylaxis in infants: is the ampule/syringe/needle method practical?*
**J Allergy Clin Immunol** 108:1040-1044, 2001. ♦♦

## Immunotherapy vs Nasal Steroids for Allergic Rhinoconjunctivitis and Asthma: Randomized Trial

IN patients with allergic rhinitis, specific immunotherapy (SIT) and nasal steroids (NS) are both effective in reducing symptoms and inflammation. This study directly compared SIT with NS for the treatment of seasonal rhinoconjunctivitis and asthma.

The study included 41 patients, mean age 29 years, with birch pollen allergy. All patients had rhinoconjunctivitis; 21 had asthma in addition. They were randomized to receive either SIT with a standardized depot preparation of birch pollen extract or NS therapy with budesonide, 400 µg/d. Before and during birch pollen season--which was very intense during the study year--bronchial hyperresponsiveness was assessed and blood eosinophil studies were performed.

Both groups had significant increases in symptom scores during birch pollen season, compared with the preseason values. During the last 2 weeks of the season, however, patients in the NS group had significantly fewer symptoms than those in the SIT group. The NS group had a significant decrease in peak expiratory flow values during pollen season, with an increase in bronchial hyperresponsiveness.

Asthmatic patients assigned to SIT did not have the typical seasonal increase in methacholine sensitivity. Asthmatic patients in the NS group had significant increases in blood eosinophils, eosinophil cationic protein, and eosinophil chemotactic activity, while those in the SIT group did not. The two treatments were similarly effective in reducing the need for rescue medication.

In patients with seasonal allergic rhinoconjunctivitis, NS therapy is more effective than a short, preseason course of SIT in alleviating symptoms. For patients with asthma in addition to rhinoconjunctivitis, SIT prevents the increase in bronchial hyperresponsiveness during pollen season, as well as the increases in blood eosinophil markers. The mechanisms of bronchial hyperresponsiveness after heavy allergen exposure differ for patients with rhinitis only compared to those with asthma, the findings suggest.

**COMMENT:** *Although these researchers were not using the aqueous extract we usually use in the United States, they did administer what should be an adequate therapeutic dose of birch pollen antigen before the start of the season. It was somewhat surprising that the patients' symptoms scores did not have a better response to SIT compared to topical NS. Symptom score data show no significant difference between NS and SIT until after week 4 of the pollen season. The fact that the subgroup with asthma who received SIT had improvement in their seasonal peak flow rates, eosinophil markers, and bronchial hyperresponsiveness indicates that SIT is truly a disease- and immune-modifying therapy.*
*S. M. F.*
*Rak S, Heinrich C, Jacobsen L, et al: A double-blinded, comparative study of the effects of short preseason specific immunotherapy and topical steroids in patients with allergic rhinoconjunctivitis and asthma.* **J Allergy Clin Immunol** 108:921-928, 2001. ♦♦

## Added Ipratropium Has No Benefit in Children Hospitalized for Acute Asthma

FOR children seen in the emergency department (ED) with severe asthma, previous studies have suggested that adding two or three doses of ipratropium bromide to $\beta_2$-agonist therapy improves lung function while reducing hospitalization rate. However, the benefits of ipratropium for children who have been admitted to the hospital from the ED remain unknown. This issue was addressed in a randomized trial.

The study included 80 patients, aged 1 to 18 years, admitted to a pediatric hospital for acute asthma exacerbation, following intensive ED treatment with albuterol, ipratropium, and corticosteroids. One group was randomized to receive nebulized ipratropium bromide in addition, 250 µg; the other received isotonic sodium chloride solution, 1 mL. The main outcome measure was clinical asthma score, measured at baseline and every 6 hours for up to 36 hours.

The two groups had similar baseline characteristics. Before enrollment, the children received an average of 6 doses of ipratropium in the ED. During the 36-hour study, they received a median of 13 doses.

Patients assigned to ipratropium or isotonic sodium chloride had similar improvement in clinical asthma scores through 36 hours. There were no differences in secondary outcomes, including $FEV_1$, or in the use of other treatments, including albuterol or systemic corticosteroids. On subgroup analysis, patients receiving three or fewer doses of ipratropium in the ED had significantly lower clinical asthma scores at 36 hours.

This randomized trial finds no benefit of added ipratropium bromide in children admitted to the hospital after intensive ED treatment for acute exacerbation of asthma. There is some evidence of benefit for children who received three or fewer doses of ipratropium in the ED, although this finding must be interpreted with caution. The authors note that most of the children in the study were less than 5 years old and unable to perform $FEV_1$ reliably.

**COMMENT:** *A number of studies suggest there is an additional benefit when ipratropium is added to nebulized albuterol for the treatment of children with severe exacerbation of asthma. These pediatricians from Canada and Ireland tried to answer the question of potential benefit from continued use of* ➤➤

*ipratropium after hospitalization for acute asthma. In this carefully performed, well-controlled study of 80 patients, there was no statistically significant benefit from the addition of ipratropium. It was of interest that a subgroup analysis suggested that children who received three or fewer doses of ipratropium in the ED benefited from continued use after hospitalization, whereas those who received more than three doses did not.*
*S. M. F.*
*Goggin N, Macarthur C, Parkin PC: Randomized trial of the addition of ipratropium bromide to albuterol and corticosteroid therapy in children hospitalized because of an acute asthma exacerbation.* **Arch Pediatr Adolesc Med** 155:1329-1334, 2001. ♦♦

## Even Without Infection, Rhinovirus Causes Proasthmatic Changes in Airway Smooth Muscle

RHINOVIRUS infection of the respiratory tract--the most common respiratory disease--is a frequent cause of asthma exacerbations. The mechanism of this effect is generally thought to involve various proinflammatory cytokines. An in vitro study was performed to assess the direct effects of RV on proasthmatic-like changes in airway smooth muscle (ASM) responsiveness, even in the absence of viral infectivity.

Cultured human ASM cells and isolated rabbit ASM tissues were treated with RV16 or RV2 serotypes. Some samples were treated with infectious RV and others with irradiated, noninfectious RV. The ASM constrictor responses to acetylcholine and relaxant responses to isoproterenol were assessed. Further studies were performed to evaluate ASM membrane $G_i$ protein expression and proinflammatory cytokine release.

Treatment with the "minor" RV2 subtype had no apparent effect on ASM responsiveness. In contrast, ASM preparations treated with RV16 showed an enhanced contractile response to the cholinergic agonist and an impaired relaxation response to the β-adrenergic agonist. Treatment with RV16 was also associated with increased $G_i$ protein expression and increased release of the proinflammatory cytokines interleukin-5 and interleukin-1β.

These proasthmatic changes occurred even in preparations treated with irradiated RV16, which showed no viral replication. They were completely prevented in samples pretreated with a neutralizing antibody against intercellular adhesion molecule-1 (ICAM-1), the endogenous host receptor for RV16 on the ASM cell surface.

The findings suggest that the proasthmatic effects of RV on ASM depend not on viral infection, but on binding between RV and its receptor on the cell surface, ie, ICAM-1. These changes--including an increased constrictor response to cholinergic stimulation and an impaired relaxation response to β-adrenoreceptor stimulation--are unrelated to proinflammatory cytokines, as previously thought. The RV-induced changes in airway function occur in the absence of any cellular damage caused by viral infectivity; asthma exacerbations might occur in the absence of any apparent clinical symptoms.

**COMMENT:** *It is no news to any practitioner that colds (URIs) commonly trigger flares of asthma. It could be assumed that the inflammatory effects of the viruses (usually Rhinovirus subtypes) on the airways cause asthma to flare--but NOOOOO! This study shows that RV16 can cause enhanced smooth muscle contractility to a cholinergic agonist, and impaired relaxation to a β-agonist, in an isolated in vitro preparation unaffected by inflammatory responses. Proasthmatic cytokines were also released by the smooth muscle tissue. Inhibition of viral replication by irradiation still caused similar effects. But the addition of antibody against ICAM-1, the host receptor for RV, completely blocked the proasthmatic effects of RV. Think of the therapeutic potential.*
*R. J. M.*
*Grunstein MM, Hakonarson H, Whelan R, et al: Rhinovirus elicits proasthmatic changes in airway responsiveness independently of viral infection.* **J Allergy Clin Immunol** 108:997-1004, 2001. ♦♦

## Echinacea Can Cause Adverse Events, Study Shows

ALTHOUGH "natural" products are commonly perceived as safe, several reports have documented hypersensitivity and toxic reactions to various forms of complementary and alternative medicine. One popular product--believed to enhance resistance to infection--is echinacea, a flowering plant of the same family as ragweed and mugwort. The authors have recently seen 5 patients with adverse reactions to echinacea. They report this experience, along with other cases of adverse reactions to echinacea.

Of the patients seen by the authors, 2 had anaphylaxis; 2 had asthma, 1 of them in response to her first-ever exposure; and 1 had a maculopapular rash. Skin prick tests were positive in 3 patients, and 3 had repeated symptoms when they tried using echinacea again.

The investigators also reviewed 51 Australian adverse drug reports in which echinacea was implications. Twenty-six of these seemed to involve IgE-mediated hypersensitivity reactions, including 4 cases of anaphylaxis, 12 of acute asthma, and 10 of urticaria or angioedema. Finally, skin testing of 100 clinic patients being evaluated for atopy showed positive reactions to echinacea in 20 cases.

As the use of echinacea continues to increase, adverse reactions to this "natural" medication will likely become more frequent. Positive skin test responses may occur even in subjects without known exposure to echinacea, which may be cross-reactive with other environmental allergens. Allergic patients should be warned that they may be at increased risk of such adverse events.

**COMMENT:** *The increasingly frequent use of alternative medicine is a growing concern. Patients who experience chronic diseases such as allergy or* ➤➤

*asthma are probably more likely than the general population to seek relief in herbal and other alternative therapies. The use of such treatments by the general population exceeds 50%, based on a variety of sources. Allergists/immunologists should be able to provide cogent advice about these therapies and to recognize potential adverse effects. The prevalence of IgE reactivity or cross-reactivity with echinacea is 20% in this Australian study of an atopic clinical population, and I suspect the findings would be similar if investigated in the United States.*
*D. K. L.*
*Mullins RJ, Heddle R: Adverse reactions associated with echinacea: the Australian experience.*
**Ann Allergy Asthma Immunol** 88:42-51, 2002. ♦♦

## Omalizumab Is Beneficial in Seasonal Allergic Rhinitis

SEASONAL allergic rhinitis is a common IgE-mediated condition that causes bothersome symptoms and is a major reason for outpatient medical visits. The recombinant humanized monoclonal anti-IgE antibody omalizumab reduces circulating free IgE levels. The safety and efficacy of omalizumab in preventing symptoms of seasonal allergic rhinitis were evaluated in a multicenter, randomized trial.

The study included 536 patients, aged 12 to 75 years, at 25 U.S. centers. All had a history of moderate to severe ragweed-induced seasonal allergic rhinitis, with a baseline IgE level of 30 to 700 IU/mL. They were randomized into four treatment groups: subcutaneous omalizumab 50, 150, or 300 mg or placebo. Treatment started just before ragweed season and continued for 12 weeks: repeated every 3 weeks in patients with IgE levels of 151 to 700 IU/mL (4 doses total) and every 4 weeks in those with IgE levels of 30 to 150 IU/mL (3 doses total). Outcome measures included daily nasal symptom severity scores, rescue antihistamine use, and rhinitis-specific quality of life score.

Nasal and ocular symptom scores were significantly lower in patients receiving omalizumab 300 mg than in patients receiving placebo. During the height of pollen season, omalizumab 150 mg was also significantly more effective than placebo. As nasal symptoms decreased, so did IgE levels and rescue antihistamine use. Patients receiving the highest dose of omalizumab had better rhinitis-specific quality of life scores--in this group, scores did not decline significantly during peak allergy season.

Omalizumab was associated with dose-dependent reductions in serum free IgE but increases in ragweed-specific IgE, apparently reflecting ragweed-specific IgE bound up in IgE-omalizumab complexes. Adverse events were similar in the omalizumab and placebo groups.

In patients with seasonal allergic rhinitis, treatment with omalizumab reduces symptoms while lowering free IgE levels. At a 300 mg dose, starting just before the onset of pollen season, omalizumab reduces nasal and ocular symptoms and the use of rescue antihistamines. Benefits in quality of life are apparent as well.

**COMMENT:** *Omalizumab is one of the many new immunologic therapies undergoing evaluation for the treatment of allergic diseases. This monoclonal anti-human IgE antibody attaches to free IgE, decreasing the majority of circulating IgE and subsequently reducing IgE receptors on basophils and mast cells. It has been studied in patients with moderate to severe asthma (with several reviews in previous* AllergyWatch *issues), and now in patients with ragweed-induced allergic rhinitis. Despite many challenges, the authors were able to demonstrate a decrease in free IgE levels and clinical improvement in ragweed-allergic patients taking omalizumab. Omalizumab may also help to further decrease the possibility of developing complications of allergic rhinitis, including asthma and chronic sinusitis.*
*A. L. L.*
*Casale TB, Condemi J, LaForce C, et al, for the Omalizumab Seasonal Allergic Rhinitis Trial Group: Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial.*
**JAMA** 286:2956-2967. ♦♦

## Atopic Children Are at Increased Risk of Frequent Wheezing and Asthma Hospitalization

SOME of the clinical heterogeneity of asthma may reflect differing causative factors. Exposure and sensitization to allergens are thought to play a key role, but few studies have examined atopy's importance as a cause of asthma in the population. The relationship between specific and general sensitization to aeroallergens and asthma was investigated in two samples of Australian children.

The analysis included a random population-based sample of 758 schoolchildren, aged 8 to 10 years, and a hospital-based sample of 78 asthmatic children. Both samples were from the Australian Capital Territory, an inland region with an urban center surrounded by grasslands. Skin-prick testing to aeroallergens was performed in both groups, while a subset of 515 of the population sample underwent spirometry.

Among the schoolchildren, 34.3% had ever experienced an episode of asthma, while 25.2% had a history of recent wheezing, 28.6% had hay fever, and 21.2% had eczema. A reduced $FEV_1$/forced vital capacity ratio--used as an indicator of airway obstruction--was more frequent among children with 4 or more recent episodes of wheezing. Univariate analysis suggested that sensitization to any allergen was significantly related to hospitalization for asthma as well as sensitization to other allergens. Among non-sensitized children, asthma risk was significantly associated with maternal smoking and parental history of asthma, but not with sex, birth weight, number of siblings, or parental education or employment.

As the frequency of wheezing increased, so did the likelihood of atopy, hay fever, or eczema. Odds ratios (ORs) for atopy increased from 3.27 for children with 1 to 3 episodes of wheezing to 8.70 for those with more than 12 episodes. Only one-third of cases of population-based asthma were attrib- ➤➤

utable to atopy, whereas the population-attributable fraction of asthma hospitalizations was nearly 90%.

This study of Australian children finds a strong association between atopy and frequent wheezing, and even more so with hospital admission for asthma. Atopy is a relatively weak contributor to infrequent wheezing or to history of asthma ever. The effects of aeroallergen sensitization on pediatric asthma depend on the severity of disease, the results suggest.

**COMMENT:** *While wheezing in infancy is not associated with atopy, asthma in 8- to 10-year-olds is quite different. This cross-sectional study reports very strong associations between atopy and both frequent wheezing (OR 8.70) and asthma hospitalization (OR 16.95). Although these data do not prove that allergic exposures are responsible for more severe asthma, they do suggest that children in this age group with severe asthma are more likely to be atopic than are children with less severe asthma.*
*S. A. T.*
*Ponsonby A-L, Gatenby P, Glasgow N, et al: Which clinical subgroups within the spectrum of child asthma are attributable to atopy?*
**Chest** 121:135-142, 2002. ♦♦

## Study Compares Therapeutic Ratios of R- and RS-Albuterol

IN the past, the $\beta_2$-agonist activity of albuterol has been attributed to the drug's R-enantiomer, with the S-enantiomer considered to have no physiologic effect. Recent studies have suggested that R-albuterol has a better therapeutic ratio than racemic (RS) albuterol. The bronchodilator and systemic effects of R-albuterol and RS-albuterol were compared in asthma patients.

The study included 20 asthma patients with asthma and at least 15% $FEV_1$ reversibility. In randomized, crossover fashion, the patients were studied while receiving R-albuterol, 6.25 to 1,600 µg; S-albuterol, 6.25 to 1,600 µg; RS-albuterol, 12.5 to 3,200 µg; or placebo. Patients received cumulative doses at 25-minute intervals with a Mefar MB-3 dosimeter. Twenty minutes after each doses, the patients' $FEV_1$, heart rate, and plasma potassium responses were assessed. At the end of each study day, patients were evaluated for any safety issues or clinically significant effects of treatment.

Forced expiratory volume in 1 second increased in dose-related fashion with both R-albuterol and RS-albuterol. In addition, at higher doses both preparations increased heart rate while reducing plasma potassium. Both R-albuterol and RS-albuterol had a 2:1 potency ratio for improvement in $FEV_1$. Like placebo, S-albuterol had no systemic effects.

The findings confirm that the R-enantiomer is responsible for the pharmacologic effects of RS-albuterol. The S-enantiomer is clinically inactive, and does not affect the therapeutic ratio of albuterol. In asthma patients with $FEV_1$ reversibility, R-albuterol and RS-albuterol have a similar therapeutic ratio.

**COMMENT:** *These authors present data questioning the hypothesis that S-albuterol is responsible for detrimental effects. Incremental dosing every 20 minutes for 3 hours was used to evaluate the various isomers of albuterol's effect on $FEV_1$, heart rate, and serum potassium levels. No detrimental effect was found with S-albuterol, and no significant difference between racemic and R-albuterol was demonstrated. Although the accompanying editorial questions the benefit of R-albuterol, I am concerned about the small number of subjects and the artificial dosing technique used to formulate these conclusions.*
*S. M. F.*
*Lötvall J, Palmqvist M, Arvidsson P, et al: The therapeutic ratio of R-albuterol is comparable with that of RS-albuterol in asthmatic patients.*
**J Allergy Clin Immunol** 108:726-731, 2001. ♦♦

## Passive Smoking at Work Linked to Respiratory Symptoms

PASSIVE smoking is a widespread problem associated with exposure to many different respiratory irritants. There are relatively few data on the effects of exposure to environmental tobacco smoke in adults. Data from the European Community Respiratory Health Survey were used to assess the respiratory effects of passive smoking in adults.

The analysis included information on 7,882 adults, aged 20 to 48 years, who had never smoked. Information on exposure to passive smoking and respiratory symptoms was gathered using a structured questionnaire; subjects at most centers underwent spirometry, methacholine challenge testing, and total and specific IgE measurement.

At 12 of the 36 study centers, more than half of subjects reported regular exposure to passive smoking. Rates of passive smoking were highest in southern and central Europe and lower in New Zealand, Australia, the United States, and Sweden. On multivariate analysis, passive smoking was related to various symptoms, including nocturnal chest tightness, shortness of breath after activity, and awakenings caused by shortness of breath. Passive smoking was also associated with increased bronchial responsiveness.

Exposure to passive smoke in the workplace was significantly associated with nearly all categories of respiratory symptoms and with current asthma. However, exposure to passive smoking at home was not associated with respiratory symptoms. Passive smoking was unrelated to total serum IgE.

This worldwide study confirms that the presence of passive smoking is high but variable. Exposure to passive smoke at work is significantly related to respiratory symptoms and increased bronchial responsiveness, though these associations are not significant for passive smoking in the home. While acknowledging the limitations of their cross-sectional study, the investigators call for efforts to reduce passive exposure to tobacco smoke, particularly in the workplace.

**COMMENT:** *The effects of passive smoking have been extensively studied in children, but less so in adults. This large cross-sectional study of 7,882 adults at 36 centers in 16 countries demonstrated the varied prevalence of passive smoking and its association with respiratory symptoms. Of special* ➤➤

*interest was the strong association between respiratory symptoms and passive smoking in the workplace, but lack of association when exposure occurred in the household. Several explanations were offered, including the possibility that household smoking may be curbed when a family member has respiratory symptoms or may occur in a sequestered part of the house, or perhaps outside.*
*E. J. B.*
*Janson C, Chinn S, Jarvis D, et al: Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey: a cross-sectional study.*
**Lancet** 358:2103-2109, 2001. ♦♦

## GERD in Young Adults Linked to Higher Rates of Asthma and Respiratory Symptoms

PREVIOUS studies have shown that gastroesophageal reflux disease (GERD) is common among patients with asthma, and suggested that the relationship may be a causative one. Most studies of the asthma-GERD relationship have been performed in highly selected referral populations. The association of GERD with asthma, sleep-disordered breathing, and other respiratory symptoms was evaluated in a population-based study.

The cross-sectional study included a random sample of 2,202 young adults, aged 20 to 48 years, from three European countries. Evaluations included questioning for asthma- and GERD-related symptoms, lung function and bronchial hyperresponsiveness testing, skin-prick tests, and a sleep questionnaire.

One hundred one subjects in the random population sample had nocturnal symptoms of GERD, a rate of 4.6%. Subjects with nocturnal GERD were more likely to be overweight and to report symptoms related to sleep-disordered breathing. The GERD group had greater peak flow variability and a higher frequency of respiratory symptoms, including wheezing, breathlessness at rest, and nighttime breathlessness. Patients with both asthma and nocturnal GERD were heavier and had a higher rate of various sleep-related symptoms.

Young adults with nighttime symptoms of GERD have increased rates of respiratory symptoms--including symptoms of obstructive sleep apnea--and asthma. The findings emphasize the upper airway narrowing or occlusion that occurs during sleep in obstructive sleep apnea syndrome and the "upper airway resistance syndrome"; in both situations, stomach acid could be drawn up into the distal esophagus by means of negative intrathoracic pressure. The relationship between GERD and asthma has potentially important implications for patient management.

**COMMENT:** *Accurately sorting out the relationships between asthma and GERD has proven difficult over the years. This large epidemiologic study, focusing on random samples of young adults, reports a strong association between self-reported nocturnal GERD and symptoms of both asthma and sleep apnea. Considering that many asthmatics have silent GERD, these results probably reflect only the effects of more severe GERD. Nevertheless, subjects reporting physician-diagnosed asthma were more than twice as likely to have nocturnal GERD symptoms than nonasthmatics. There were no significant associations between asthma medications (including β-agonists and theophylline) and GERD.*
*S. A. T.*
*Gislason T, Janson C, Vermeire P, et al: Respiratory symptoms and nocturnal gastroesophageal reflux: a population-based study of young adults in three European countries.* **Chest** 121:158-163, 2002. ♦♦

## Study Compares Allergy and Sensitization Rates Among Twins

STUDIES of twins provide unique opportunities for assessing the relative contributions of genetic and nongenetic factors to allergic diseases. Previous studies have compared rates of asthma for monozygotic and dizygotic twins. This study analyzed the concordance of self-reported allergic diseases as well as total and allergen-specific IgE levels among twins.

The analysis included adult female twins, aged 18 to 72 years, from the St. Thomas's U.K. Adult Twin Registry: 340 monozygotic pairs and 533 dizygotic pairs. All women completed a questionnaire regarding allergic diseases. Testing for total and house dust mite- , grass- , and cat-specific IgE was performed in 282 monozygotic pairs and 270 dizygotic pairs.

Both monozygotic and dizygotic twins had a high concordance rate for "any allergy," although half of all affected monozygotic pairs were discordant for this highly prevalent variable. On specific IgE testing for mite and pollen, concordance rates among monozygotic twins were higher for younger pairs than for older pairs. For dizygotic twins, age had no effect on concordance rates. Even when a pair were concordant for specific IgE to an allergen, it did not necessarily mean that both members were sensitized to the same allergens. Monozygotic twins had higher concordance rates for hay fever, eczema, and specific IgE than dizygotic twins, but not for asthma or allergies. Analysis of within-pair correlations of log-transformed IgE suggested heritability of about 60%; the remaining 40% was attributed to unshared environmental factors.

This twin study suggests that sensitization to common aeroallergens and allergic diseases is significantly affected by genetics. Nevertheless, even genetically identical monozygotic twins can have differing expressions of atopic diseases. Thus in predisposed subjects, environmental factors appear to have the major impact on patterns of sensitization and manifestations of allergic disease.

**COMMENT:** *These researchers took advantage of the U.K. Adult Twin Registry to investigate the interrelationship of allergic disease among twin* ➤➤

*pairs. It was of interest that the within-pair correlation for total serum IgE levels implied a hereditary contribution of 60% in the monozygotic twins. The discordance rates of 30% among monozygotic pairs for specific allergen sensitivities (grass and mite) suggest that nongenetic factors are important influences in the manifestation of allergic disease. The fact that these genetically identical twins varied in their expression of atopy suggests that environmental rather than genetic factor are of prime importance in determining the pattern of sensitization and associated allergic diseases. The nature vs nature debate continues.*
*S. M. F.*
*Strachan DP, Wong J, Spector TD: Concordance and interrelationship of atopic diseases and markers of allergic sensitization among adult female twins.*
**J Allergy Clin Immunol** 108:901-907, 2001. ♦♦

## Hair Bonding Glue Linked to Anaphylaxis in a Latex-Allergic Patient

HAIR bonding and hair extensions have become very popular among people wishing to change the style or length of the hair or for management of localized or diffuse hair loss. Hair extensions are fixed to the individual's scalp using commercial glues consisting of pigments, antioxidants, and natural rubber latex (NRL). A patient with systemic anaphylaxis caused by NRL in hair glue is reported.

The patient was a 37-year-old woman with a previous history of local reactions to NRL condoms and gloves. A friend used a commercial hair bond glue to attach braids to her scalp. At the first exposure, she had mild scalp dysesthesias. At a second exposure, 1 month later, she had localized itching followed by generalized pruritus, diffuse urticaria, angioedema, and tachycardia. The reaction resolved after the patient removed the glue from her scalp and took 25 mg of diphenhydramine. She had a positive skin test to the glue, a positive RAST to latex, and positive serologic reactions to latex allergens. Analysis of the hair bond glue showed an antigen pattern similar to that of ammoniated latex.

Commercially available hair bond glues can cause allergic reactions in patients sensitized to latex. These reactions are potentially serious and may be underrecognized; one anaphylactic death associated with a hair extension has been reported. Allergists, cosmetologists, and patients with NRL allergy should be aware of these potential reactions.

**COMMENT:** *As our understanding of latex allergy increases, case reports such as these will help clinicians recognize and appropriate treat unusual causes of anaphylaxis.*
*A. M.*
*Cogen FC, Beezhold DH: Hair glue anaphylaxis: a hidden latex allergy.*
**Ann Allergy Asthma Immunol** 88:61-63, 2002. ♦♦

## Anaphylaxis to Isosulfan Blue During Sentinel Node Biopsy

ISOSULFAN blue is widely used with lymphangiography to visualize the lymph vessels, and recently has come into use for sentinel lymph node biopsy. Few previous reports have described anaphylactic reactions to this dye. A 60-year-old woman with breast cancer was undergoing sentinel node biopsy using subcutaneously administered isosulfan blue 1%, 5 mL. Five minutes later, she became hypotensive and hypoxemic, with oxygen saturation dropping to 74%. She also had wheezing and urticaria. She required treatment with IV epinephrine and emergency intubation. Her blood pressure normalized over time, and she was extubated after 4 hours. The patient's history included a rash in response to penicillin and local swelling with lidocaine during dental treatment; she had not previously been exposed to isosulfan blue.

A second patient also reacted to isosulfan blue during sentinel lymph node biopsy, including prolonged hypotension. Both patients had positive skin-test results to isosulfan blue, but not to any other agent tested.

Isosulfan blue, used for sentinel node biopsy or other diagnostic procedures, can cause anaphylactic reactions. Neither patient in this report had previously been exposed to this dye, suggesting sensitization to a cross-reactive antigen--possibly phenophthalein.

**COMMENT:** *Lymphangiography continues to be necessary for evaluation of suspected malignancies. This well-done report of two cases of dye-induced anaphylaxis further adds to our understanding of a rare but important occurrence.*
*A. M.*
*Laurie SA, Khan DA, Gruchalla RS, Peters G: Anaphylaxis is isosulfan blue.*
**Ann Allergy Asthma Immunol** 88:64-66, 2002. ♦♦

## How Do Food Allergies Affect Quality of Life for Children and Families?

FOOD allergy is a common and sometimes severe problem in young children. The impact of food allergy on children's quality of life was assessed using the Children's Health Questionnaire, which provides information on parents' perceptions on their child's physical and psychosocial functioning.

Two hundred fifty-three parents (response rate 63%) of food-allergic children completed this instrument, along with a specific allergy-related questionnaire. The children's mean age was 11 years; 68% were allergic to one or two foods, the rest to three or more foods. Ninety-six percent of the children were seeing an allergist, and 93% had a prescription for epinephrine. As a group, the parents had frequent contact with their children's school to discuss food allergy--54% once yearly and 21% once monthly.

Compared with scores in a normal population, these children with food allergy had low ➤➤

scores for general health, although much of the difference was attributed to coexisting asthma and atopic dermatitis. Scores for emotional impact on the parent and limitation on family activities were also significantly reduced, and these were unaffected by associated atopic disease. Children with three or more food allergies had reduced scores on more scales than those with fewer allergies.

Food allergies have a significant impact on several areas of quality of life for affected children and their families. In addition to the children's general health, food allergy has consequences for the parents' emotional state and the family's activities. The impact is even greater for children with additional food allergies and atopic comorbidity. A limitation of the study is that respondents were recruited from a food allergy support group.

**COMMENT:** *The results of this survey serve as an important reminder that food allergy has a significant impact on both the child's and the family's quality of life. The thoughtful editorial by Dr. James that accompanies this article further reminds us of the important issues that weigh heavily on the minds of children and parents and provides helpful suggestions on how to address these issues.*
*A. M.*

*Sicherer SH, Noone SA, Muñoz-Furlong A: The impact of childhood food allergy on quality of life.* **Ann Allergy Asthma Immunol** 87:461-464, 2001. ♦♦

## Fluticasone Added to Cefuroxime is Beneficial in Rhinosinusitis

PATIENTS with chronic, persistent sinusitis are commonly treated with intranasal corticosteroids and antibiotics. However, the benefits of adding corticosteroids to antibiotics for acute rhinosinusitis in such patients are unclear.

In the Ceftin and Flonase for Sinusitis (CAFFS) Trial, 95 patients with rhinosinusitis were randomized to receive intranasal fluticasone propionate, two puffs (200 µg total) in each nostril once daily for 21 days, or placebo. All patients had a history of recurrent sinusitis or chronic rhinitis with radiographic or endoscopic evidence of acute infection. In addition to fluticasone or placebo, both groups received xylometazoline hydrochloride, two puffs in each nostril twice daily for 3 days; and cefuroxime axetil, 250 mg twice daily for 10 days. Clinical success rates were assessed at 10, 21, and 56 days' follow-up.

Eighty-eight patients completed the study. The rate of clinical success--defined as a patient report of cure or much improved--was 93.5% in the fluticasone group vs 73.9% in the placebo group. Median time to clinical success was 6 days in the fluticasone group vs 9.5 days in the placebo group. Adding fluticasone to antibiotics cured 1 additional patient for every 6 treated. Other benefits of fluticasone included faster improvement in subjective work performance and fewer recurrences.

This randomized trial supports the addition of intranasal fluticasone to antibiotic therapy for acute rhinosinusitis in patients with a history of chronic rhinitis or recurrent sinusitis. Adjunctive intranasal corticosteroids yield a higher cure rate and shorter recovery time than xylometazoline and cefuroxime alone.

**COMMENT:** *Nasal topical corticosteroid therapy is frequently used in subjects with sinusitis, although studies investigating the efficacy of this treatment have been inconclusive. The current double-blind study is a needed addition to the clinical literature. Significantly, patients were recruited from both primary care and specialty clinics, providing a probable diversity of severity and chronicity. A criticism of the study is that two-thirds of the patients were diagnosed with a Waters view of the sinus, an imaging study with limitations. The authors discuss this issue. The groups differed within 2 days with respect to work improvement. Clinical improvement was 3.5 days more rapid with nasal corticosteroid. Satisfyingly, clinical observations have been validated by clinical trial data.*
*D. K. L.*

*Dolor RJ, Witsell DL, Hellkamp AS, et al: Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFFS Trial: a randomized controlled trial.* **JAMA** 286:3097-3105. ♦♦

## BMI Is an Independent Risk Factor for Asthma

IN recent decades, obesity and asthma have both become increasingly prevalent. There are few data on the relationship between body mass index (BMI) and asthma. This potential association was analyzed using data from a large, representative U.S. population sample.

The study included 7,505 respondents, aged 4 to 17 years, to the Third National Health and Nutrition Examination Study (NHANES III). Data on BMI, breast-feeding status, and presence of asthma and hay fever were collected in interviews with parents. Skin-prick tests were performed to determine the presence of atopic sensitization.

The prevalence of both asthma and atopy increased with BMI. For asthma, prevalence increased from 8.7% at the lowest quartile of BMI, to 9.3%, to 10.3%, to 14.9% at the highest quartile. For atopy, prevalence increased from 48.6%, to 50.5%, to 53.0%, to 53.2%, from the lowest to the highest quartiles of BMI. Body mass index remained significantly associated with asthma after adjustment for confounders, adjusted odds ratio 1.77. In contrast, BMI was not independently associated with atopy. The relationship between BMI and asthma was unaffected by sex and ethnicity.

These NHANES III data suggest that high BMI is an independent risk factor for asthma in children and adolescents. The mechanism of this relationship is unknown; there is evidence to suggest that obesity is associated with upregulation of inflammatory processes, and that it increases airway responsiveness via a mechanical impact on the airway smooth muscle. ➤➤

**COMMENT:** *There is a parallelism between the rising prevalence of obesity reported in the United States and United Kingdom and the simultaneous rise in asthma and atopy. This study suggests that BMI may be an independent risk factor for the development of asthma in both sexes and across ethnic groups. Evidence in this regard is mounting and may account for the higher asthma risk in inner-city populations.*
*E. J. B.*
*von Mutius E, Schwartz J, Neas LM, et al: Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III.* **Thorax** 56:845-850, 2001. ♦♦

## Study Supports Persistence of Cow's Milk Protein-sensitive Enteropathy in Older Children

MOST previous reports on cow's milk protein intolerance suggest that the condition resolves by age 5. However, the authors recently reported evidence of persistent or new-onset cow's milk protein-sensitive enteropathy (CMSE)--including typical endoscopic and histopathologic findings--in older children. They report further investigations of the morphologic and immunohistochemical findings of CMSE.

The subjects were drawn from a consecutive series of 6- to 14-year-old children referred to a pediatric gastroenterologist for evaluation of persistent GI symptoms. Blinded challenge studies--performed after 2 weeks complete elimination of milk protein from the diet--identified 15 children with a definite diagnosis of CMSE. The clinical, endoscopic, histologic, and immunohistochemical findings were compared to those of 12 children with suspected CMSE, 11 with celiac disease, and 12 control children.

The endoscopic findings in children with CMSE included visible lymphonodular hyperplasia of the duodenal bulb, while biopsy examination revealed lymphoid follicles without villous atrophy. On immunohistochemical studies of the bulb biopsies, CMSE was associated with increased densities of intraepithelial CD3+ and γδ+ T cells. The latter finding was the best discriminator between the various groups studied.

The findings support the existence of CMSE in school-aged children. The authors recommend careful evaluation, including milk challenge studies and endoscopic and histologic evaluations, of children with suspected CMSE. The immunohistochemical findings are consistent with local antigen intolerance on the GI mucosa.

**COMMENT:** *Some experts have felt that CMSE is a condition of infancy, sometimes associated with milk allergy, sometimes with milk intolerance. This report from Finland provides new information related to CMSE, in that older children (aged 6 to 14 years) either had persistent GI symptoms since infancy or developed new symptoms related to cow's milk ingestion. All 27 patients improved with milk elimination and 12 developed GI symptoms during a 7-day home "blind" milk challenge.*
*J. A. A.*
*Kokkonen J, Haapalahti M, Laurila K, et al: Cow's milk protein-sensitive enteropathy at school age.*
**J Pediatr** 139:797-803, 2001. ♦♦

## What's New?

## What's New on the Effects of the Farm Environment on Allergy/Asthma Risk?

IN view of the increasing interest in the role of the farm environment on the development of asthma and allergies, the Editors of *AllergyWatch* call the reader's attention to three recent studies of this issue from *Clinical and Experimental Allergy*, along with a related editorial.
Barnes M, Cullinan P, Athanasaki P, et al: Crete: does farming explain urban and rural differences in atopy? Clin Exp Allergy 31:1822-1828, 2001.
Filipiak B, Heinrich T, Schäfer T, et al: Farming, rural lifestyle and atopy in adults from southern Germany--results from the MONICA/KORA study Augsburg. **Clin Exp Allergy** 31:1829-1838, 2001.
Heinrich J, Gehring U, Douwes J, et al: Pets and vermin are associated with high endotoxin levels in house dust. **Clin Exp Allergy** 31:1839-1845, 2001.
Braun-Fahrländer C: The role of the farm environment and animal contact for the development of asthma and allergies (editorial).
**Clin Exp Allergy** 31:1799-1803, 2001.

**COMMENT:** *In the past several years, the "filth hypothesis" has emerged to help explain why living on farms early in life appears to afford some protection from developing atopic diseases. These three studies add to our understanding of this phenomenon, but they by no means prove causation. For example, the study by Heinrich et al demonstrates that homes with a household pet have higher house dust endotoxin levels. This suggests that endotoxin exposure, with its resultant Th1 allergen response, explains the previously reported reduced risk of asthma in homes with furry pets. However, other studies have suggested that pet exposure is associated with a modified Th2 response, which is not consistent with an endotoxin effect. The exact environmental influence(s) and the immunologic consequences that reduce the risk of atopy remain unproven.*
*S. A. T.* ♦♦

## How Do Inhaled Steroids Affect Voice in Asthma Patients?

HOARSENESS is a common and bothersome upper-airway side effect of inhaled corticosteroids. This is a highly subjective symptom that ➤➤

may go unnoticed by many patients. One laryngoscopic study has found subtle signs of steroid-induced myopathy of the vocal cords, even before changes in voice quality become audible. Objective acoustic analysis techniques were used to measure the effects of initial steroid therapy on vocal function in asthma patients.

The study included 87 steroid-naive patients with asthma. Seventy-seven were randomized to one of four regimens of inhaled budesonide dipropionate; another 10 asthma patients who used only occasional bronchodilator therapy were studied as controls. Voice recordings for acoustic analysis were obtained at baseline and at intervals from 1 to 16 weeks of treatment. The acoustic measures of interest were jitter and shimmer, defined as cycle-to-cycle variation in the time period and of the voice signal, respectively.

At baseline, mean jitter and shimmer scores were both significantly lower in the bronchodilator-only control group than in the active treatment groups. Inhaled budesonide therapy had no significant effect on mean jitter score. Mean shimmer score decreased significantly with active treatment, with no significant differences between groups. The improvement in shimmer persisted through 4 months of inhaled budesonide therapy.

The simple acoustic analysis technique used in this study can detect subtle changes in voice quality associated with asthma and its treatment. This study suggests that inhaled budesonide therapy actually improves voice shimmer scores in steroid-naive asthma patients. The effects of treatment on voice appear consistent across the steroid dosing schedules and devices used in this study.

**COMMENT:** *While inhaled corticosteroids have a well-known potential to cause dysphonia, little is known about the upper airway in asthmatics. This study showed consistent improvements in subclinical voice acoustics among steroid-naive asthmatic subjects treated with beclomethasone (1,000 µg/d) for 4 months. Additional studies are necessary to determine the mechanism of this observation. It is unlikely to involve a direct steroid effect on the glottis, since the associations in this study were unaffected by the use of a spacer device.*
*S. A. T.*
*Balter MS, Adams SG, Chapman KR: Inhaled beclomethasone dipropionate improves acoustic measures of voice in patients with asthma.*
**Chest** 120:1829-1834, 2001. ♦♦

## Cetirizine Is Again Superior to Loratadine in Controlled Pollen Challenge Study

MULTICENTER trials have been performed to compare cetirizine and loratadine for the control of pollen-induced allergic rhinitis. However, limitations of these studies have included variation or undocumented pollen levels between study centers. Such variation can be controlled by the use of an environmental exposure unit (EEU). A placebo-controlled comparison of cetirizine and loratadine in an EEU found that cetirizine had a faster onset of action and provided greater symptom relief than loratadine. Another EEU study was performed to confirm these results in a larger group of patients.

Three hundred sixty patients with seasonal allergic rhinitis (SAR) were randomized to receive cetirizine 10 mg/d, loratadine 10 mg/d, and placebo, using the same design as in the previous study. The three treatments were compared in terms of onset of action and symptom relief. The use of a EEU ensured consistent pollen counts; across study cohorts, mean ragweed pollen count was around 3,500 grains/$m^3$.

Mean overall reduction in total symptom complex scores was about 25% with cetirizine, compared to 11% with loratadine and 5% with placebo. As in the previous study, cetirizine was significantly more effective than loratadine, and both active treatments were significantly more effective than placebo. Cetirizine again had an earlier onset of action than loratadine.

The results replicate the previous EEU study showing the greater effectiveness of cetirizine over loratadine for the treatment of SAR. In response to a controlled pollen challenge, cetirizine consistently offers greater symptom reduction with a faster onset of action.

**COMMENT:** *This article supports previous clinical studies of the efficacy of cetirizine in SAR. The use of the environmental exposure unit further supports the "real world" differences among antihistamines that can be observed in clinical practice.*
*A. M.*
*Day JH, Briscoe M, Rafeiro E, et al: Comparative onset of action and symptom relief with cetirizine, loratadine, or placebo in an environmental exposure unit in subjects with seasonal allergic rhinitis: confirmation of a test system.*
**Ann Allergy Asthma Immunol** 87:474-481, 2001. ♦♦

## In Vitro Study Supports Steroid-Sparing Effect of Clarithromycin in Asthma

MACROLIDE antibiotics may be given in an attempt to reduce glucocorticoid (GC) requirements in patients with severe steroid-dependent asthma. The mechanism of this steroid-sparing effect may involve an anti-inflammatory effect of macrolides, in addition to inhibition of methylprednisolone clearance. The immunomodulatory effects of clarithromycin, and its potential synergistic effect with dexamethasone, were examined in a preliminary study.

Seven patients with well-controlled, mild to moderate asthma received open-label treatment with clarithromycin, 500 mg twice daily for 10 days. Before and after treatment, blood samples were obtained for lymphocyte stimulation assays. The ability of clarithromycin to suppress phytohemagglutinin-induced lymphocyte activation--in the ➤➤

presence and absence of dexamethasone--was examined in vitro.

At baseline, clarithromycin alone did not significantly suppress T-lymphocyte activation. However, it did render lymphocytes more sensitive to suppression by dexamethasone, with a 6-fold shift in the dexamethasone dose-response curve. After 10 days of clarithromycin treatment, the inhibitory concentration causing a 50% reduction in proliferation for dexamethasone alone was significantly reduced, with the effect of increased GC sensitivity. The inhibitory effect of clarithromycin alone was increased as well, while the synergistic effect of clarithromycin and dexamethasone in suppressing lymphocyte stimulation was preserved.

The results suggest that the macrolide antibiotic clarithromycin and the GC dexamethasone have a synergistic effect in suppression of lymphocyte activation. The authors call for a placebo-controlled study in patients with severe, steroid-dependent asthma to determine whether the steroid-sparing effect of clarithromycin is truly independent of its antimicrobial effect.

**COMMENT:** *The debate concerning the value of macrolide antibiotic therapy combined with systemic glucocorticoid therapy for asthma continues, with divergent results in the literature. This is an interesting study but very preliminary, since the data are based on in vitro lymphocyte proliferation to a nonspecific mitogen. Nevertheless, the clinical need for agents that amplify or supplement the effects of corticosteroid therapy make such information of greater interest. The final macrolide-asthma chapter has not been written.*
*D. K. L.*

*Spahn JD, Fost DA, Covar R, et al: Clarithromycin potentiates glucocorticoid responsiveness in patients with asthma: results of a pilot study.*
**Ann Allergy AsthmaImmunol** 87:501-505, 2001.

## REVIEWS OF NOTE

Kaplan AP: Chronic urticaria and angioedema.
**N Engl J Med** 346:175-179, 2002.

**COMMENT:** *Dr. Kaplan is to be commended for a career peering into the near-darkness of chronic urticaria. In this article, he uses a simple clinical vignette to make a few cogent points about this frustrating condition: its pathogenesis(es) (40% to 50% autoimmune?); the clinical tests that are worth doing (few to none); and the treatment (palliation until it subsides). He suggests further investigation into the effects of leukotriene inhibitors and newer immunosuppressants.*
*R. J. M.*

Sicherer SH: Clinical implications of cross-reactive food allergens.
**J Allergy Clin Immunol** 108:881-890, 2001.

**COMMENT:** *Diagnosing food allergies is hard enough, but made even more vexing by the increasing realization that many disparate biologic entities share homologous allergenic proteins. To wit: latex and avocado, crustaceans and house dust mites, birch pollen and apples, and many others. How often are peanuts (legumes) and tree nuts (nonlegumes) co-allergenic? How risky is goat's milk in a patient with cow's milk allergy? There is much to be learned, but this review article is quite helpful to the practitioner facing these questions from patients today.*
*R. J. M.*

Shrewsbury S, Hallett C: Salmeterol 100 µg: an analysis of its tolerability in single- and chronic-dose studies.
**Ann Allergy Asthma Immunol** 87:465-473, 2001.

**COMMENT:** *This review and the accompanying editorial provide helpful reassuring data regarding the long-term safety of salmeterol. Although many physicians expressed concerns based on theoretic issues, in practice salmeterol has proven extremely safe and effective.*
*A. M.*

Babu KS, Arshad SH, Holgate ST: Anti-IgE treatment: an update.
**Allergy** 56:1121-1126, 2001.

**COMMENT:** *This is a superb review of the mode of action and attenuation of the late asthmatic response by omalizumab. The three large studies conducted in the United States are analyzed and compared with studies in the European Union, South Africa, and Australia.*
*E. J. B.*

Brusasco V, Crimi E: Methacholine provocation test for diagnosis of allergic respiratory diseases.
**Allergy** 56:1114-1120, 2001.

**COMMENT:** *These authors do an excellent job in reviewing the complex physiology of airway narrowing in response to methacholine challenge and its relationship to airway inflammation.*
*E. J. B.*

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