

ALLERGYWATCH®

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

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

Volume 2, Number 5

September-October 2000

New Form of Hereditary Angioedema Affects Females Only

THE autosomal dominant disease hereditary angioedema (HAE) is caused by an inherited deficiency of C1 inhibitor function. Affected patients have recurrent angioedema without urticaria; other causes of recurrent angioedema are recognized as well. However, some patients have idiopathic angioedema, in which the symptoms cannot be attributed to any known cause. A unique form of HAE associated with normal C1-inhibitor function and affecting women only is reported.

Of a series of 574 patients with recurrent angioedema of the skin, 283 had associated attacks of abdominal pain and/or upper airway obstruction. Ninety-four of this group had C1-inhibitor deficiency and/or a positive family history. Functional C1-inhibitor deficiency was discovered in 84 patients from 49 families. No other family members were affected in 11 cases.

Ten women from 10 families did not meet criteria for either HAE I or HAE II and had normal plasma

C1-inhibitor protein concentrations and function. Further investigation identified 26 more affected family members, all of whom were women. Clinical features included relapsing skin swelling, abdominal pain, and laryngeal edema, but none of the patients had urticaria. Age at onset ranged from 1 to 63 years. Several patients were treated with C1-inhibitor concentrate, to no effect. A few patients responded to danazol. Biochemical studies confirmed that all patients with the variant form of HAE had normal C1-inhibitor protein concentrations.

This new form of HAE is clinically similar to HAE I and II, but affects women only and is associated with normal C1-inhibitor protein concentration and function. The variant HAE appears to follow an X-linked dominant mode of inheritance. The authors propose the term HAE III. Possible mediators of the attacks of vasodilation and edema include bradykinin, a C2 fragment, or fibrin-split products.

COMMENT: Two types of hereditary angioedema (HAE) have been distinguished. HAE I occurs in 85% of >>>

CONTENTS

- | | |
|--|---|
| 1 New Form of Hereditary Angioedema Affects Females Only | 7 Prevalence of Asthma in Middle Age Has Doubled |
| 2 "Clinically Silent" Gastroesophageal Reflux Is Common in Asthma Patients | 7 Meloxicam Is Tolerated by NSAID-Sensitive Patients |
| 2 Fatal and Near-Fatal Asthma Attacks: Patient Characteristics | 8 COX-2 Inhibitors Linked to Reduced Renal Function |
| 3 What Are the Uses of Quantitative IgE Antibody Assays? | 8 New ELISA Measures Eosinophil-Derived Neurotoxin |
| 3 Comparison of Fexofenadine and Loratadine for Seasonal Allergic Rhinitis | 9 Relapsed Childhood Asthma Is More Severe Than Adult-Onset Asthma |
| 4 Rhinovirus Infection Increases ICAM-1 Expression in Asthma | 9 Clarithromycin Reduces Bronchial Inflammation in Asthma |
| 4 Diesel Exhaust Particles Cause Inflammatory Airway Response | 10 Zileuton Cannot Prevent Reactions in Aspirin-Sensitive Asthma Patients |
| 5 Low-Dose Fluticasone Is Superior to Zafirlukast as Initial Therapy for Persistent Asthma | 10 Inhaled Glucocorticoids Differ in Transcriptional Potencies |
| 5 Study Shows Cross-Reactivity Between Celery and Birch Profilins | 10 Th2 Cytokine Inhibitor Is Beneficial in Steroid-Dependent Asthma |
| 6 Outdated Epinephrine Autoinjectors Lose Effectiveness | 11 Nasal Air Sampler Measures Individual Exposure to Allergens |
| 6 Intranasal Corticosteroids Do Not Increase Cataract Risk | 11 Is Inhaled Nitric Oxide Effective in Status Asthmaticus? |
| 6 Montelukast Plus Loratadine Is Effective in Seasonal Allergic Rhinitis | 12 REVIEWS OF NOTE |

EDITOR

Emil J. Bardana, Jr., M.D.
Portland, OR

ASSOCIATE EDITOR

Anthony Montanaro, M.D.
Portland, OR

ASSISTANT EDITORS

Michael S. Blaiss, M.D.
Memphis, TN

Joann Blessing-Moore, M.D.
Palo Alto, CA

James R. Bonner, M.D.
Birmingham, AL

Richard J. Morris, M.D.
Minneapolis, MN

Jay M. Portnoy, M.D.
Kansas City, MO

Stephen A. Tilles, M.D.
Portland, OR

Dennis K. Ledford, M.D.
Tampa, Florida

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
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- Mayo Clinic Proceedings

"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. Subscription rates - U.S., Individual \$90.00 Outside the U.S.: \$115.00, Residents, Fellows, Students within the U.S.: \$60.00, outside the U.S., add \$18.00, bulk subscription pricing available upon request of the publisher. Send subscription inquiries to AllergyWatch®, P.O. Box 381, Mt. Savage, Maryland 21545. 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. No portion of this publication may be reproduced in any manner either written or by retrieval system without the written permission of the Publisher. The reviews and commentary expressed within this publication are solely those of the editorial board and not those of the ACAAI; additional data and opinions should be obtained through reading the full original content. Copyrighted by The American College of Allergy, Asthma & Immunology. Printed in the U.S.A. ISSN 1521-2440.

patients and plasma concentrations of C1 inhibitor are 5% to 30% of normal. In HAE II, concentrations are normal or raised. The two forms are clinically indistinguishable. A new form of HAE is described in 36 patients. This form is associated with recurrent angioedema, affects only women, involves other family members, and is never associated with urticaria. Patients have normal C1 inhibitor and C4 concentrations in plasma. C1-inhibitor concentrate has no therapeutic effect, but danazol has been found to be effective in selected cases.

E. J. B.

Bork K, Barnstedt S-E, Boch P, Traupe H: Hereditary angioedema with normal C1-inhibitor activity in women. Lancet 356:213-217, 2000. ♦♦

"Clinically Silent" Gastroesophageal Reflux Is Common in Asthma Patients

SOME patients have asthma that is triggered by gastroesophageal reflux, yet have none of the classic symptoms of reflux. Previous studies have suggested that identification and treatment of this group of patients can improve asthma control in difficult-to-control cases. The prevalence and severity of gastroesophageal reflux were assessed in 26 asthma patients without reflux symptoms. All patients had stable asthma. They underwent esophageal manometry with 24-hour esophageal pH testing. Thirty age-matched asthmatic patients with symptomatic gastroesophageal reflux were studied for comparison.

Sixty-two percent of the patients without reflux symptoms had abnormal results on 24-hour esophageal pH testing. None of the demographic factors studied predicted this finding, including nocturnal asthma. Reflux disease was just as severe in the asymptomatic patients as in the symptomatic asthma group. The asymptomatic group actually had higher amounts of proximal esophageal acid. The symptomatic patients were more likely to be taking theophylline and had more severe asthma than the asymptomatic group.

This study finds a high rate of clinically silent gastroesophageal acid reflux in patients with asthma. Twenty-four-hour esophageal pH monitoring is necessary to detect this condition, which cannot be predicted by demographic variables.

COMMENT: This study demonstrated that 62% of asthmatics who did not have gastroesophageal reflux symptoms had demonstrable acid in their proximal esophagus according to 24-hour pH study. When compared to asthmatics who had symptoms of gastroesophageal reflux, they did tend to have milder asthma and were more frequently treated with medications that lead to gastroesophageal reflux such as theophylline. The data appear to justify the conclusion that a 24-hour pH study needs to be done to identify asymptomatic asthmatics. However, such a study is not clinically practical in all patients. What the study really shows is that gastroesophageal reflux should be considered in patients who have asthma that is not readily controlled even in the absence of symptoms. A therapeutic trial of an aggressive antireflux regimen—with observation for changes in asthma symptoms or medication requirements—is clearly indicated under those circumstances.

J. M. P.

Harding SM, Guzzo MR, Richter JE: The prevalence of gastroesophageal reflux in asthma patients without reflux symptoms.

Am J Respir Crit Care Med 162:34-39, 2000. ♦♦

Fatal and Near-Fatal Asthma Attacks: Patient Characteristics

RECENT reports suggest a rising incidence of fatal or near-fatal asthma attacks occurring outside the hospital in young patients. These ➤➤

attacks may be described by such terms as brittle asthma, out-of-a-clear-blue-sky asthma, or sudden asphyxic asthma. The characteristics of 45 patients with fatal or near-fatal asthma attacks were analyzed.

The patients were identified through a survey of 400 regional asthma specialists. There were 25 cases of near-fatal asthma: 13 males and 12 females, mean age 29 years. About three-fourths of the near-fatal attacks occurred at home or en route to the hospital. Sixty percent developed within less than 3 hours. There were 20 cases of fatal asthma: 16 females and 4 males, mean age 22 years. Eighty percent of these attacks occurred within less than 3 hours. Nearly all of the patients died at home, en route to the hospital, or in a public place.

All patients were using short-acting inhaled corticosteroids, with 60% showing good to excellent compliance. However, about half had adverse psychosocial factors, such as self-denial and poor care. Eighty percent were classified as having labile or brittle asthma. Reported triggers for the attacks included respiratory infections and ingested, inhaled, or injected allergens.

Near-fatal and fatal out-of-hospital asthma attacks can occur in young patients with stable asthma who are compliant with their prescribed inhaled corticosteroids. The authors call for a national case registry to determine the demographic and clinical characteristics of patients experiencing these attacks. It has been suggested that regular inhaled β -agonist use in select patients with labile or brittle asthma may cause increased bronchial hyperreactivity, thus predisposing to sudden attacks in the face of an offending trigger.

COMMENT: Dr. Hannaway provides us with very valuable and practical insights on patients who experience fatal and near-fatal asthma. With currently available pharmacotherapy we assume that asthma control is only "a prescription away." This regional survey reminds us that almost half of these frightening episodes apparently occur in compliant patients maintained on chronic anti-inflammatory therapy. The problem of undertreatment with oral corticosteroids appears to account for approximately one-fourth of episodes. As the accompanying editorial points out, asthma control requires *system* wide changes with a focus on both patients *and* provider education.

A. M.

Hannaway PJ: Demographic characteristics of patients experiencing near-fatal and fatal asthma: results of a regional survey of 400 asthma specialists.

Ann Allergy Asthma Immunol 84:587-593, 2000. ♦♦

What Are the Uses of Quantitative IgE Antibody Assays?

THERE is a long history of debate over the use of immunoassays for allergen-specific IgE antibodies. Newer assays allow reporting of IgE antibodies in mass units, although the clinical significance of these measurements remains open to question. Current thinking about the benefits of the newer quantitative IgE antibody assays is reviewed.

All of the assays include a solid phase for sepa-

ration of bound and unbound IgE antibodies. The allergen source materials should always be specified, and reagents should be produced without losing critical allergens. All of the assays have quality assurance specifications to ensure proper performance of the reagent. Safety regulations address equipment calibration, characterization of the allergen reagents, documentation of the reagents' specificity, and assessment of reproducibility within and between lots. The interassay coefficient of variation must be no greater than 15%; laboratories are encouraged to take part in intralaboratory proficiency testing programs.

The new assays may be useful in perinatal identification of infants at risk of atopy. Some studies have evaluated sensitization to chicken egg as a marker for the development of atopy. The results suggest that a positive result is nonsensitive but highly specific for later allergic rhinitis and aeroallergen sensitization. Assays for food-specific IgE appear to have high predictive value in detecting the presence of food sensitization. Quantitative levels of IgE to inhalant allergens can accurately depict an individual patient's sensitivities and serve as an indicator of current allergic exposures. After allergen avoidance measures have been put in place, follow-up measurements may show reduced allergen-specific IgE antibody levels. The role of quantitative IgE antibody assays in managing allergy to latex, insect venom, or other allergens remains to be determined.

Although skin tests remain the most important technique for demonstrating IgE antibody to allergens, IgE antibody assays can be diagnostically useful in many situations. Regardless of the test used, its clinical relevance must be established by the history and patient examination. The two techniques cannot be regarded as interchangeable; both have important advantages in specific circumstances.

COMMENT: For years, a debate has raged over the relative merits of skin prick testing versus in vitro serum testing for the diagnosis of allergies. Finally the answer is in: it depends. This article (accompanied by a cogent editorial) summarizes the varied situations in which one or the other method is favored. For those looking for a simple answer, you will be disappointed. Skin prick testing is not obsolete, but the RAST is not anathema.

R. J. M.

Yunginger JW, Ahlstedt S, Eggleston PA, et al: Quantitative IgE antibody assays in allergic diseases.

J Allergy Clin Immunol 105:1077-1084, 2000. ♦♦

Comparison of Fexofenadine and Loratadine for Seasonal Allergic Rhinitis

NO previous studies have compared antihistamines for efficacy and their effects on quality of life in patients with seasonal allergic rhinitis (SAR). This randomized, double-blind trial compared fexofenadine HCl 120 mg, loratadine 10 mg, and placebo in 688 patients with SAR. All patients had a positive skin test to grass and/or tree pollen and a symptomatic response to antihistamines. No other drug treatment was allowed during the study. Symptoms assessed were sneezing; rhin- ➤➤

orrhea; itchy nose, palate, and/or throat; and itchy, watery, and/or red eyes. The main efficacy outcome was change in the mean 24-hour total symptom score from baseline. Quality of life was assessed using the Rhinoconjunctivitis Quality of Life Questionnaire.

On intention-to-treat analysis, both active treatments significantly reduced the mean total symptom score. Compared with loratadine, fexofenadine HCl brought greater improvement in itchy, watery or red eyes and in nasal congestion. For nasal congestion, loratadine was not significantly better than placebo. However, overall effectiveness was similar for the two active-treatment groups. Fexofenadine improved quality of life scores to a greater extent than loratadine, and the difference was considered clinically significant. Adverse events were similar among groups.

For patients with SAR, fexofenadine HCl 120 mg and loratadine 10 mg are both effective and well-tolerated treatments. However, fexofenadine performs better in relieving eye symptoms and nasal congestion and in improving quality of life. Fexofenadine relieves symptoms throughout the 24-hour dosing interval, including trough levels. Although the quality-of-life improvement with fexofenadine is small, it is clinically worthwhile.

COMMENT: In this large multicenter study both loratadine 10 mg and fexofenadine 120 mg taken once daily proved effective in the treatment of seasonal allergic rhinitis. The news is that fexofenadine was superior to loratadine in improving itching, watery red eyes, nasal congestion, and patients' quality of life. Although oral antihistamines are not usually thought to relieve nasal congestion, this is the third published study to demonstrate such an effect for fexofenadine. Of note, the fexofenadine dose used in this study was one-third less than the once-daily dose recently launched in the United States.

J. R. B.

van Cauwenberge P, Juniper EF, and the Star Study Investigating Group: Comparison of the efficacy, safety, and quality of life provided by fexofenadine hydrochloride 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. *Clin Exp Allergy* 30:891-899, 2000. ♦♦

Rhinovirus Infection Increases ICAM-1 Expression in Asthma

RESPIRATORY viruses—especially rhinoviruses—are thought to play an important role in asthma exacerbations. In vitro studies have shown that rhinovirus infection in airway epithelial cells is followed by upregulation of intercellular adhesion molecule-1 (ICAM-1) expression. This molecule serves not only as a receptor for rhinovirus but also as an adhesion molecule for inflammatory cells. The current study investigated the role of ICAM-1 in pathogenesis of rhinovirus-induced asthma exacerbations.

The study included 25 nonsmoking, non-steroid-treated patients with atopic asthma. Each patient underwent 2 weeks of treatment with either inhaled budesonide, 800 µg bid, or placebo. They were

then inoculated with rhinovirus 16 (RV16). Bronchoscopy was performed 2 days before and 6 days after RV16 inoculation. Bronchial biopsy specimens were obtained for immunohistochemical measurement of RV16.

The staining studies showed the most intense epithelial ICAM-1 staining on basal cells, with less intense staining on parabasal cells and no staining on ciliated or goblet cells. After RV16 infection, ICAM-1 expression in the bronchial epithelium increased to a similar extent in both groups. The increase in ICAM-1 expression was not related to an epithelial intactness score.

Inoculation with a common cold virus increases ICAM-1 expression in the bronchial epithelium of patients with atopic asthma. The upregulation of ICAM-1 is not prevented by glucocorticoid treatment. Rhinovirus may promote asthma exacerbations by increasing the expression of its own receptor. New treatments are needed to interrupt this process.

COMMENT: Rhinovirus has been repeatedly implicated as a major cause of asthma exacerbations, though confirming the mechanism has been elusive. This study demonstrates in vivo that rhinovirus 16 induces expression of its own receptor (ICAM-1) in the bronchial epithelium, and this effect is not prevented by inhaled corticosteroid treatment. The authors do not report whether the patients treated with inhaled corticosteroids experienced fewer asthma symptoms after rhinovirus inoculation.

S. A. T.

Grünberg K, Sharon RF, Hiltermann TJN, et al: Experimental rhinovirus 16 infection increases intercellular adhesion molecule-1 expression in bronchial epithelium of asthmatics regardless of inhaled steroid treatment. *Clin Exp Allergy* 30:1015-1023, 2000. ♦♦

Diesel Exhaust Particles Cause Inflammatory Airway Response

DIESEL exhaust particles (DEP) are an important component of air pollution, and have been linked to reversible decrements in lung function. The effects of DEP on clinical measures and airway inflammation were studied in 10 healthy, nonsmoking volunteers. In randomized, crossover fashion, the subjects were exposed for 2 hours to air or to DEP at a concentration of 200 µg/m³ particulate matter of less than 10 µm aerodynamic diameter. Analyses included serial spirometry; assessment of pulse, blood pressure, exhaled CO, and methacholine reactivity; sputum induction; and plasma cytokine assays.

Exhaled CO increased after DEP exposure, peaking at 1 hour: levels were 2.9 ppm while breathing air vs 4.4 ppm during exposure to DEP. After 4 hours of DEP exposure, sputum neutrophil count and myeloperoxidase were both significantly increased. There were no elevations in peripheral blood inflammatory markers. The subjects reported no symptoms related to DEP exposure.

Exposure to DEP produces an airway ➤➤

inflammatory response in normal volunteers. This response is characterized by activated neutrophil influx and an increase in exhaled CO. The DEP concentration used in this study is similar to that encountered in ambient air in large cities or in occupational settings.

COMMENT: Diesel exhaust particles have been suspected of causing inflammation when inhaled. In this study, healthy volunteers were exposed to DEPs in a controlled manner. Since the particles were less than 10 μm in size, one would expect them to penetrate into the distal airways. Though there were no changes in pulmonary or cardiac parameters measured, neutrophils and neutrophil myeloperoxidase in sputum were increased for up to 4 hours after the challenge. It is known that persons who already have pulmonary inflammation frequently develop respiratory symptoms when exposed to particles similar to those used in this study. Because of that, they tend to limit their exposure by remaining indoors on days with high pollution levels. Normal individuals apparently do not develop symptoms and therefore they often permit such exposure. This makes the results of this study even more disturbing.

J. M. P.

Nightingale JA, Maggs R, Cullinan P, et al: Airway inflammation after controlled exposure to diesel exhaust particulates. *Am J Respir Crit Care Med* 162:161-166, 2000. ♦♦

Low-Dose

Fluticasone Is Superior to Zafirlukast as Initial Therapy for Persistent Asthma

CURRENT National Institutes of Health guidelines suggest that leukotriene modifiers are an acceptable alternative to low-dose inhaled corticosteroids as initial therapy for control of persistent asthma. Few studies have addressed this issue, however. This randomized trial compared inhaled fluticasone propionate, 88 μg twice daily, with oral zafirlukast, 20 mg twice daily, for the treatment of persistent asthma. The study included 451 patients, 12 years of age or older, who remained symptomatic while taking short-acting β_2 -agonists only. Efficacy and safety were assessed according to National Asthma, Education, and Prevention Program guidelines.

Morning FEV₁ increased by 0.42 L over baseline with fluticasone vs 0.20 L with zafirlukast. Morning peak expiratory flow increased by 49.94 L/min with fluticasone vs 11.68 L/min with zafirlukast, while evening peak expiratory flow increased by 38.91 vs 10.50 L/min, respectively. The reduction in albuterol use was 2.39 puffs/d with fluticasone vs 1.45 puffs/d with zafirlukast. Percentage of nights without awakenings increased by 21.2% vs 8.0% with zafirlukast. Fluticasone also brought a greater improvement in percentage of symptom-free days. There was no difference in the rate of asthma exacerbations or adverse events.

For patients with persistent asthma, low-dose fluticasone propionate appears to be more effective as initial therapy than zafirlukast. Pulmonary function and asthma symptom status are improved to a signifi-

cantly greater extent with fluticasone. As reflected by current treatment guidelines, inhaled corticosteroids are the best long-term controller medications for patients with persistent asthma.

COMMENT: The 1997 NIH guidelines for the treatment of asthma did not resolve the proper place of leukotriene inhibitors. Particularly in "mild persistent" asthmatics, it is not certain whether they should all receive inhaled corticosteroids or whether leukotriene inhibitors might do as well. This parallel study of mild to moderate asthmatics compared the efficacy of low-dose fluticasone (88 μg bid) with standard-dose zafirlukast (20 mg bid) over 12 weeks. Although both regimens produced improvements over baseline, all objective and subjective short-term measures clearly favored fluticasone.

R. J. M.

Bleecker ER, Welch MJ, Weinstein SF, et al: Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma.

J Allergy Clin Immunol 105:1123-1129, 2000. ♦♦

Study Shows Cross-Reactivity Between Celery and Birch Profilins

PROFILINS are ubiquitous proteins described as panallergens. Profilin-specific IgE antibodies may account for the occurrence of cross-reactivity to botanically unrelated sources of allergen. Some patients with allergy to celery also have IgE reactivity with profilin. The investigators cloned celery profilin to assess its immunologic characteristics and its cross-reactivity with birch pollen profilin, Bet v 2.

On DNA sequencing studies, a 399 bp reading frame coding for a 133-amino acid protein was identified. The protein, with a calculated molecular weight of 14.3 kDa, had 71% to 82% identity with other plant profilins that are known allergens. Immunoblotting showed specific IgE antibodies to the protein in 7 of 17 patients with celery allergy. Inhibition experiments showed high cross-reactivity between celery and birch pollen profilins.

Celery profilin plays an important role in allergy to celery and is highly homologous to birch pollen profilin. The authors propose the term Api g 1 for celery profilin. Cross-reactivity between homologous profilins may account to birch pollinosis and associated allergy to celery. Recombinant Api g 4 may be useful in studying cross-reactivity between plant profilins.

COMMENT: Profilins, a family of proteins involved in signal transduction and actin binding, have similar structures in different plants. Immunologic cross-reactivity between plant profilins may explain some instances of patient hypersensitivity to botanically unrelated pollens and foods. Cross-reactivity such as this may also explain reports of improvement in food allergy in patients given pollen immunotherapy.

J. R. B.

Scheurer S, Wangorsch A, Hausteiner D, Veiths S: Cloning of the minor allergen Api g 4 profilin from ➤➤

celery (*Apium graveolens*) and its cross-reactivity with birch pollen profilin Bet v 2. Clin Exp Allergy 30:962-971, 2000. ♦♦

Outdated Epinephrine Autoinjectors Lose Effectiveness

EPINEPHRINE autoinjectors—such as EpiPen and EpiPen Jr—play a key role in prompt treatment of anaphylaxis. These devices include several features to prevent degeneration of epinephrine, including an acidic solution with an antioxidant and a light-resistant container. There are few data on the pharmacologic activity and toxicity of epinephrine degradation products. These factors were assessed in a sample of outdated EpiPen and EpiPen Jr autoinjectors. The devices were obtained from patients at risk of anaphylaxis; all were unused. Epinephrine content and bioavailability were measured in 28 EpiPen and 6 EpiPen Jr devices.

The devices were tested 1 to 90 months after their expiration date. The patients were aware of the issues of expiration date and optimal storage conditions, and about three-fourths said they checked the expiration date regularly. On inspection, the autoinjectors were intact and functioning, although the plastic sheaths showed signs of damage or wear. In most cases, the epinephrine was not discolored and contained no precipitates. However, the bioavailability of epinephrine from outdated devices was significantly reduced. The longer the time past the expiration date, the less the epinephrine content.

Patients at risk of anaphylaxis should make sure that their epinephrine autoinjectors are not past their expiration date. The longer the injector is out-of-date, the lower its epinephrine content. However, as long as the epinephrine is not discolored and does not contain precipitates, outdated autoinjectors can be used if needed.

COMMENT: Recently the FDA has questioned the determination of expiration dates for medications. Simons, Gu, and Simons evaluated outdated autoinjectors of epinephrine and found their bioavailability is significantly decreased compared with nonoutdated ones. Physicians should make sure that patients keep a current autoinjector to get maximal benefit during an anaphylactic episode. The authors do point out that using an expired autoinjector is definitely better than risking no treatment.

M. S. B.

Simons FER, Gu X, Simons KJ: Outdated EpiPen and EpiPen Jr autoinjectors: past their prime? J Allergy Clin Immunol 105:1025-1030, 2000.

Intranasal Corticosteroids Do Not Increase Cataract Risk

MORE and more patients are taking intranasal corticosteroids for the treatment of allergic rhinitis. Long-term oral steroid use carries an increased risk of

ocular side effects, including cataract development. This retrospective study assessed the risk of cataract formation in intranasal steroid use. A British research data base was used to compare the rate of cataract formation in approximately 88,000 intranasal corticosteroid users, 99,000 oral corticosteroid users, and 99,000 subjects with no corticosteroid exposure. A nested case-control analysis was performed to control for confounding factors.

For both intranasal corticosteroid users and nonexposed controls, cataract occurred at an incidence rate of 1.0/1,000 person-years. The rate was significantly higher, 2.2/1,000 person-years, for oral corticosteroid users.

Intranasal corticosteroid use does not appear to increase the risk of cataract. Although confirmatory studies are needed, the results suggest that cataract formation is not a major concern in deciding on the relative value of intranasal corticosteroids for allergic rhinitis.

COMMENT: Concerns about the side effects of long-term use of intranasal corticosteroids have been growing. A major fear in prescribing intranasal corticosteroids is cataract formation. Derby and Maier reviewed records from a large-scale U.K. pharmaceutical data base and found no evidence of an increased incidence of cataracts among users of intranasal corticosteroids, compared with nonusers. Obviously, prospective studies are needed to confirm this information. Nevertheless, this report is reassuring to medical providers and their patients.

M. S. B.

Derby L, Maier WC: Risk of cataract among users of intranasal corticosteroids.

J Allergy Clin Immunol 105:912-916, 2000. ♦♦

Montelukast Plus Loratadine Is Effective in Seasonal Allergic Rhinitis

ALLERGIC rhinitis is a common condition for which many different types of medications may be appropriate. Important proinflammatory mediators in this disease include histamine and cysteinyl leukotrienes. The cysteinyl leukotriene receptor antagonist montelukast—alone or in combination with the H₁-receptor antagonist loratadine—was evaluated for use in the treatment of seasonal allergic rhinitis.

The double-blind, randomized trial included 460 adult patients with seasonal allergic rhinitis from 12 centers. The patients received montelukast alone, 10 or 20 mg; loratadine alone, 10 mg; montelukast 10 mg plus loratadine 10 mg; or placebo. All medications were taken once daily in the evening. Symptoms and other outcomes were evaluated before and after 2 weeks of treatment.

Daytime nasal symptoms score was improved to a significantly greater extent with montelukast plus loratadine than with placebo or with either agent alone. The combination treatment also brought significantly greater improvement in eye symptoms, nighttime symptoms, individual daytime nasal symptoms, global evaluations, and rhinoconjunctivitis quality-of-life score. All treatments were well tolerated. ➤➤

The combination of montelukast plus loratadine has at least additive clinical benefits in patients with seasonal allergic rhinitis. This is the first trial to assess the efficacy of a cysteinyl leukotriene receptor antagonist plus an H₁-receptor antagonist for allergic rhinitis. The addition of montelukast does not increase the rate of adverse events.

COMMENT: Numerous cells and mediators are responsible for the symptoms of allergic rhinitis. Meltzer et al. examined the role of combination therapy with an H₁ antagonist and a leukotriene receptor antagonist in the treatment of seasonal allergic rhinitis to determine if blocking both mediators adds additional clinical benefit. For daytime nasal symptoms and other endpoints, the combination was statistically better than either drug alone or placebo with no increase in adverse effects. This information is exciting for rhinitis management, though studies comparing this combination to antihistamine/decongestant combinations and intranasal corticosteroids are needed.

M. S. B.

Meltzer EO, Malmstrom J, Lu S, et al: Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. *J Allergy Clin Immunol* 105:917-922, 2000. ♦♦

Prevalence of Asthma in Middle Age Has Doubled

THE recent increase in asthma prevalence among children is well demonstrated. As these children age, a corresponding increase in the rate of adult asthma is expected. Data on two generations of adult subjects were analyzed to assess changes in asthma prevalence from the 1970s to the 1990s.

The study included survey data on adult residents of two Scottish towns. At both times, respondents were asked about asthma, hay fever, and respiratory symptoms. A 1972-76 survey included data from 1,477 married couples aged 45 to 64 years, while a 1996 survey included responses from 2,338 offspring of the original couples, aged 30 to 59 years. The prevalences of asthma, hay fever, and respiratory symptoms were compared for 1,708 parents and 1,124 offspring, aged 45 to 54 years.

Standardized for age and sex, the prevalence of asthma among never-smokers rose from 3.0% in the 1970s to 8.2% in the 1990s. The prevalence of hay fever rose from 5.8% to 19.9%, respectively. Among ever-smokers, the prevalence of asthma rose from 1.6% in the 1970s to 5.3% in the 1990s while the prevalence of hay fever rose from 5.4% to 15.5%. Most of the increase in asthma prevalence was related to atopic asthma, ie, asthma in the presence of hay fever. The prevalence ratio of atopic asthma was 2.52, compared with 1.00 for nonatopic asthma.

Survey data from two successive generations suggest that the prevalence of asthma among middle-aged adults has more than doubled since the 1970s. Most of this trend is related to atopy, as reflected by

hay fever symptoms. The observed increase in atopic asthma does not appear to result from increased diagnostic awareness.

COMMENT: Many epidemiologic studies have confirmed an increased prevalence of asthma in the pediatric population over the last several decades. Will this trend continue into adulthood? This Scottish study surveying a middle-aged population once in the seventies and once in the nineties found a 2-fold increase in asthma prevalence over the 20-year period. It appears that most of this increase is related to atopy. The increase in adult asthmatics should lead to more studies to determine whether aggressive management of childhood asthma and allergies can decrease the adult prevalence. These data also demonstrate the need for more asthma specialists with the aging of the population.

M. S. B.

Upton MN, McConnachie A, McSharry C, et al: Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. *BMJ* 321:88-92, 2000. ♦♦

Meloxicam Is Tolerated by NSAID-Sensitive Patients

NONSTEROIDAL anti-inflammatory drugs (NSAIDs) are a common cause of adverse drug reactions, particularly for patients with chronic urticaria or asthma. The adverse effects of NSAIDs are thought to result from inhibition of the constitutive cyclo-oxygenase isoform COX-1. The new arthritis drug meloxicam selectively inhibits the COX-2 isoform, which is induced by pro-inflammatory stimuli. A large group of patients with NSAID sensitivity were studied for their ability to tolerate meloxicam.

The study included 177 patients with a history of adverse reactions to NSAIDs. Eighty-three percent had cutaneous reactions, urticaria and/or angioedema. Other reactions included respiratory symptoms in 4% and Stevens-Johnson syndrome in 2%. Thirty-nine percent had had only a single reaction, usually to acetylsalicylic acid.

In single-blind, placebo-controlled fashion, the patients were challenged with oral meloxicam, given in doses of 1.9 mg followed 1 hour later by 5.6 mg. Just 2 patients had a positive reaction, a rate of about 1%. Both reactions were cutaneous in nature.

The selective COX-2 inhibitor meloxicam appears to be well-tolerated by patients with a history of NSAID sensitivity. For patients with a history of urticaria and/or angioedema in response to NSAIDs—even those with reactions to multiple types of NSAIDs—meloxicam has a very low rate of cross-reactivity.

COMMENT: The management of pain or arthritis in subjects with NSAID intolerance is a common clinical problem. The FDA-approved prescribing infor- ➤➤

mation cautions against the use of selective COX-2 inhibitors—celecoxib and rofecoxib—in subjects with NSAID intolerance. Reports are available indicating the reaction risk is lower with these selective COX-2 inhibitors. This article describes single-blind challenge of NSAID-sensitive subjects with meloxicam, a newly available, relatively selective COX-2 inhibitor. The reaction rate was 1.1%, with relatively mild cutaneous reactions accounting for the two adverse effects. However, only 12.9% of the population had ever experienced respiratory symptoms following NSAID ingestion. Individuals with respiratory symptoms are at greater risk of serious adverse effects on subsequent administration. The relative reaction risk with meloxicam, celecoxib, or rofecoxib administration in NSAID-sensitive subjects is probably much lower than with nonselective COX inhibitors. Caution is still necessary, however, particularly in subjects with asthma.

D. K. L.

Quarantino D, Romano A, Di Fonso M, et al: Tolerability of meloxicam in patients with histories of adverse reactions to nonsteroid anti-inflammatory drugs.

Ann Allergy Asthma Immunol 84:613-617, 2000. ♦♦

COX-2 Inhibitors Linked to Reduced Renal Function

THE new cyclo-oxygenase-2 (COX-2) inhibitors, such as rofecoxib, specifically target the COX-2 isoform, which is induced by inflammation. Traditional nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit both COX-1 and COX-2, have well-known renal adverse effects. Studies in mice and humans suggest that specific COX-2 inhibition may also affect renal function. This study assessed the effects of COX-2 inhibition with rofecoxib on renal function in elderly patients.

The study included 75 healthy patients aged 60 to 80 years. Those taking any drug known to affect renal function, including low-dose aspirin or other NSAIDs, were excluded. All patients were following a low-sodium diet. In a single-dose study, 15 patients were randomized to receive rofecoxib 250 mg, which is 5 to 20 times higher than the recommended dose; indomethacin 75 mg; or placebo. In a multiple-dose study, 60 patients took either rofecoxib 12.5 or 25 mg/d; indomethacin 50 mg tid; or placebo.

In response to a single dose, glomerular filtration rate decreased by 0.23 mL/s with rofecoxib and 0.18 mL/s with indomethacin. In the multiple-dose study, both doses of rofecoxib reduced iothalamate clearance to a significantly greater extent than placebo. There was only a trend toward reduced iothalamate clearance with indomethacin. Changes in creatinine clearance were less pronounced; changes in serum electrolytes were generally small and nonsignificant. In the multiple-dose study, 1 patient taking indomethacin had a serious adverse event related to a perforated viscus.

This study suggests that the effects of COX-2 inhibition on renal function are similar to those of conventional, nonselective NSAIDs. The use of a low-sodium diet in this study may have enhanced the effects of COX inhibition by making renal function more dependent on prostaglandins. The COX-2 inhibitors should be

used cautiously in patients with risk factors for renal insufficiency, such as congestive heart failure, diuretic use, or cirrhosis.

COMMENT: This is an important study for all practicing physicians who evaluate patients who receive NSAIDs. The growth of COX-2 inhibitors continues to be meteoric. While there is a general consensus in the medical community that these agents are safer, they clearly pose potential risks. This study emphasizes the potential for renal impairment. Previous reports have also highlighted the possibility of anaphylactic reactions. In the final analysis, we must remember that while these drugs appear to have a good safety record, selected high-risk patients must be treated cautiously.

A. M.

Swan SK, Rudy DW, Lasseter KC, et al: Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet: a randomized, controlled trial. Ann Intern Med 133:1-9, 2000. ♦♦

New ELISA Measures Eosinophil-Derived Neurotoxin

SERUM eosinophil cationic protein (ECP) concentration is a potentially useful marker of airway inflammation in asthma. However, difficulties in measuring ECP have hindered its clinical application. Among the other cationic proteins secreted by activated eosinophils is eosinophil-derived neurotoxin (EDN), sometimes termed eosinophil protein X. This 18 to 21 kD single-chain protein has been proposed as a marker of eosinophilic inflammation. The authors report the development and evaluation of a new enzyme-linked immunosorbent assay (ELISA) specific for blood and urinary EDN.

The assay was developed using EDN purified from pooled urine from healthy volunteers, to which polyclonal and monoclonal antibodies were raised. The resulting sandwich ELISA detected human EDN concentrations as low as 0.62 ng/mL. There was no evidence of cross-reactivity with ECP or other eosinophil granule cationic proteins. Studies in progressively diluted samples showed good linearity. When purified EDN was added to serum samples, recovery rates of 85% to 110% were achieved. Patients with asymptomatic asthma had significantly higher median EDN concentrations than healthy controls: 36.9 vs 19.1 ng/mL in serum, 23.0 vs 14.5 ng/mL in plasma, and 118./2 vs 19.1 ng/mL in urine. The increased EDN levels in asthma patients were significantly correlated with the peripheral blood eosinophil count, though not with total serum IgE.

The new ELISA provides reliable measurements of EDN in serum, plasma, and urine. The assay uses a monoclonal antibody that recognizes both the glycosylated and deglycosylated forms of EDN and a polyclonal antibody that recognizes only the glycosylated form. The EDN ELISA may aid in studying the role of eosinophils in bronchial asthma and other diseases.

COMMENT: A practical immunologic marker for monitoring inflammatory activity in asthma has been >>>

lacking, due in part to limitations in standardizing results. This ELISA for eosinophil-derived neurotoxin appears to correlate with eosinophilic inflammation and may better withstand the rigors of test validation than other proposed markers.

S. A. T.

Morioka J, Kurosawa M, Inamura H, et al: Development of a novel enzyme-linked immunosorbent assay for blood and urinary eosinophil-derived neurotoxin: a preliminary study in patients with bronchial asthma.

Int Arch Allergy Immunol 122:49-57, 2000. ♦♦

Relapsed Childhood Asthma Is More Severe Than Adult-Onset Asthma

SEVERAL studies have documented the rising rate of asthma in children and young adults. Longitudinal studies of childhood asthma suggest that symptoms commonly persist into adulthood, or relapse after a symptom-free interval. Disease characteristics were compared in two groups of adult patients: 84 who reported childhood asthma and 235 with asthma onset in adulthood. Both groups were 20 to 42 years old; those with other chronic pulmonary diseases, inhaled steroid treatment, or nonstable asthma were excluded. Childhood asthma was defined as that beginning before age 12 and remitting before age 18, with at least a 5-year period without asthma symptoms or treatment.

The frequency of asthma attacks was less than 1 per month for one-third of the adult-onset group vs 14% for patients reporting childhood asthma. The childhood asthma group had more frequent impairment of respiratory function: mean FEV₁ % of predicted was 80.3% in the childhood asthma group vs 86.7% in the adult-onset group. Mean forced midexpiratory flow (FEF₂₅₋₇₅) was 53.2% vs 72.4% of predicted, respectively. The childhood asthma group were more likely to report that the onset of their asthma was related to allergy and that their asthma attacks were triggered by allergy. Other factors related to childhood asthma relapsing in adulthood were male sex; lower spirometric values, particularly those related to smaller airways; sensitization to airborne allergens such as *Dermatophagoides pteronyssinus* and *D. farinae*; and maternal history of atopic dermatitis.

Among young adults with asthma, the severity of disease is greater for those with a history of childhood asthma. Values for FEV₁ and FEF₂₅₋₇₅ are particularly low in patients with childhood asthma relapsing in adulthood, in relation to the severity of childhood asthma. The results show high internal consistency, and suggest that childhood asthma can recur in adulthood even after an adolescent remission.

COMMENT: This study describes the characteristics of asthma in 235 young adults and compares these features with 84 patients with childhood-onset asthma that relapsed in adulthood. The latter group had a more severe form of asthma. In particular, FEV₁ and FEF₂₅₋₇₅ were extremely low and related to severity of childhood asthma. It seems likely that significant functional abnormalities persist during apparent "remission" and may

reflect ongoing inflammation. This study should alert allergists to follow childhood asthmatics very carefully during late adolescence, despite the appearance of being "symptom-free."

E. J. B.

Ségala C, Priol G, Soussan D, et al: Asthma in adults: comparison of adult-onset asthma with childhood-onset asthma relapsing in adulthood. Allergy 55:634-640, 2000. ♦♦

Clarithromycin Reduces Bronchial Inflammation in Asthma

CLARITHROMYCIN and other 14-membered macrolide antibiotics reportedly have an antiasthmatic effect. These agents have been used long-term as an alternative therapy for asthma; however, the mechanism of their antiasthma effect remains unknown. The effects of clarithromycin on bronchial responsiveness to methacholine were studied in 17 adult patients with stable, mild to moderate asthma. They were randomized to receive 200 mg of clarithromycin or placebo twice daily for 8 weeks. Methacholine provocation testing was performed before and after treatment. At the same time, blood and sputum eosinophil counts and eosinophil cationic protein (ECP) levels were measured.

Methacholine PC₂₀ values were significantly higher in patients receiving clarithromycin: mean log PC₂₀-methacholine value was 2.96 in the clarithromycin group vs 2.60 in the placebo group. The clarithromycin group also had a significantly greater reduction in general symptom score. Clarithromycin was associated with significant reductions in blood and sputum eosinophil counts and sputum ECP level. There were no significant changes in FVC or FEV₁.

The findings confirm the anti-inflammatory effect of clarithromycin, including suppression of eosinophilic infiltration in patients with asthma. The results warrant further investigation of the possible uses of clarithromycin as an antiasthma medication.

COMMENT: Data from a variety of sources, along with clinical experience, suggest that macrolide antibiotics have an anti-inflammatory effect in addition to their antibacterial action. This purported dual action is not unique to macrolides—the efficacy of trimethoprim/sulfamethoxazole has been attributed to both anti-inflammatory and antibacterial effects. This paper suggests that clarithromycin improves asthma and mitigates airway inflammation by suppressing eosinophil recruitment, activation, or survival. Additional studies are needed to validate these observations for asthma in general. Clinicians may consider macrolide therapy in select subjects with asthma, but the selection of appropriate patients for this therapy remains guesswork.

D. K. L.

Amayasu H, Yoshida S, Ebana S, et al: Clarithromycin suppresses bronchial hyperresponsiveness associated with eosinophilic inflammation in patients with asthma.

Ann Allergy Asthma Immunol 84:594-598, 2000. ♦♦

Zileuton Cannot Prevent Reactions in Aspirin-Sensitive Asthma Patients

LEUKOTRIENES (LTs) appear to play an important role in respiratory reactions to aspirin, or acetylsalicylic acid (ASA). This suggests that treatment with the 5-lipoxygenase inhibitor zileuton might prevent respiratory reactions to ASA. Previous studies in patients with ASA-sensitive respiratory disease have suggested that pretreatment with ASA can prevent reactions to aspirin challenge. This study assessed the ability of zileuton to prevent ASA-induced respiratory reactions.

The subjects were 6 patients with a confirmed reaction during previous oral ASA challenge. They began taking zileuton 600 mg qid 7 days before and continuing throughout oral ASA challenge. The challenges were made in single-blind, escalating-dose fashion. The ASA challenge produced a naso-ocular reaction in all 6 patients, at ASA doses of 45 to 325 mg. Despite zileuton pretreatment, 4 of the 6 patients had bronchospasm, with FEV₁ decreasing by 19% to 53%. In 3 of these 4 patients, a larger dose of ASA was required to provoke the reaction. Reactions to ASA were associated with a sharp increase in urine LTE₄.

Zileuton pretreatment dose not prevent upper respiratory reactions in patients with aspirin-sensitive asthma. The researchers had hoped that zileuton would allow "silent desensitization" to ASA, allowing desensitization to be conducted in an outpatient setting. Further studies are needed to see if this worthwhile goal can be achieved.

COMMENT: The role of leukotriene modifiers continues to be explored. While it is clear that these agents are useful as monotherapy or in combination with inhaled corticosteroids in some patients, they do not provide adequate protection from the effects of NSAIDs in sensitive patients. This well-done study clearly indicates that NSAIDs may cause significant, potentially life-threatening reactions in patients on leukotriene modifiers. This is an important message for all physicians that needs to be shared with all patients with demonstrated or potential NSAID sensitivity.

A. M.

Pauls JD, Simon RA, Daffern PJ, Stevenson DD: Lack of effect of the 5-lipoxygenase inhibitor zileuton in blocking oral aspirin challenges in aspirin-sensitive asthmatics.

Ann Allergy Asthma Immunol 85:40-45, 2000. ♦♦

Inhaled Glucocorticoids Differ in Transcriptional Potencies

RECENT years have brought great advances in our understanding of the mechanisms by which inhaled glucocorticoids (GCs) reduce inflammation. Through *trans*-activation, they increase transcription of genes taking part in either beneficial or unwanted effects. Working via *trans*-repression, they reduce expression of genes for inflammatory mediators. Five inhaled GCs

were compared for their *trans*-activation potency using a stable transfectant of HeLa S3 cells with a GC response element-dependent luciferase gene. *trans*-Repression potency was compared using A549 human lung epithelial cells transfected with an activator protein-1- or nuclear factor κ B-dependent luciferase gene.

Of the GCs tested, fluticasone propionate had the greatest transcriptional potency, followed by budesonide and triamcinolone acetate, then beclomethasone dipropionate and flunisolide. Except for beclomethasone, *trans*-activation potency in this assay was significantly correlated with the GC's ability to induce glucocorticoid-inducible enzyme tyrosine aminotransferase in hepatoma tissue culture cells. Fluticasone propionate also had the greatest *trans*-repression potency, followed by budesonide, then beclomethasone dipropionate, triamcinolone acetonide, and flunisolide. An assay measuring release of the cytokine RANTES yielded the same order of potency.

These assays help in predicting the ability of GCs to produce clinical benefits and adverse effects. Agents with low capacity to activate transcription have few side effects *in vivo*, while those with greater *trans*-repression capacity have greater anti-inflammatory effects.

COMMENT: Many methods have been used to determine the relative potencies of glucocorticoids (GC) used for asthma treatment. The problem is that many rely on measures that are only peripherally related to their anti-inflammatory effects, such as cutaneous vasoconstriction. By measuring *trans*-activation and *trans*-repression of genes involved in GC activity, the authors were able to show a relationship with side effects and inflammatory cytokines in HeLa cells. The determined rank order was fluticasone propionate > budesonide and triamcinolone acetonide > beclomethasone dipropionate and flunisolide. This corresponds roughly with that determined in several clinical trials. This makes it possible to make such a determination for new GCs and to improve our understanding of the basic physiology of such agents. In addition, side effect potentials for new agents might be measured before their introduction into clinical trials. The days when one considers 1 μ g of an inhaled corticosteroid to be equivalent to 1 μ g of another are now officially over.

J. M. P.

Jaffuel D, Demoly P, Cougat C, et al: Transcriptional potencies of inhaled corticosteroids.

Am J Respir Crit Care Med 162:57-63, 2000. ♦♦

Th2 Cytokine Inhibitor Is Beneficial in Steroid-Dependent Asthma

CYTOKINES with a Th2-like profile play a key role in the pathogenesis of asthma, perhaps through the effects of interleukin (IL)-4, IL-13, and IL-5 in stimulating IgE production, mucosal mastocytosis, and eosinophilia. The selective Th2 cytokine inhibitor suplatast tosilate was assessed for its steroid-sparing effect in patients requiring high-dose inhaled cor- ➤➤

corticosteroids to control asthma symptoms.

This randomized, double-blind trial included 85 patients with moderate to severe asthma who took at least 1,500 µg/d of inhaled beclomethasone dipropionate. They received with suplatast tosilate, 100 mg 3 times daily, or placebo for 8 weeks. Adding suplatast tosilate to inhaled corticosteroid increased FEV₁ to a significantly greater extent than adding placebo. Asthma symptoms, variation in peak expiratory flow, and serum eosinophil cationic protein and IgE also showed greater improvement with active treatment. During a steroid-reduction phase, the placebo group showed a progressive reduction in peak expiratory flow, compared with no change in the suplatast tosilate group. There were few side effects.

Suplatast tosilate can improve pulmonary function and symptom control in patients with moderate to severe, steroid-dependent asthma. As a result of these benefits, the inhaled corticosteroid dosage can be reduced without compromising disease control. The steroid-sparing effects of this Th2 cytokine inhibitor must be studied in other groups of asthma patients.

COMMENT: This Japanese double-blind, randomized, parallel-group study evaluated 77 patients with moderate to severe asthma taking high doses of inhaled beclomethasone (1,500 µg/d or more). Patients were treated with suplatast tosilate (ST), a selective Th2 cytokine inhibitor, at doses of 100 mg 3 times daily or placebo. Patients treated with ST showed improved pulmonary function, symptoms, diurnal variation in peak expiratory flow, serum eosinophil cationic protein, and total IgE. There were minimal adverse effects. Since this study focused on only a small subset of asthmatics, its results are not generalizable. Future studies with higher doses of ST may be more compelling.

E. J. B.

Tamaoki J, Kondo M, Sakai N, et al: Effect of suplatast tosilate, a Th2 cytokine inhibitor, on steroid-dependent asthma: a double-blind randomised study. *Lancet* 356:273-278, 2000. ♦♦

Nasal Air Sampler Measures Individual Exposure to Allergens

CURRENT patient-worn air samplers are limited in their ability to monitor individual allergen exposure. To overcome these limitations, the investigators have developed a personal air sampler. The device is worn just inside the nose, extending back into the nasal vestibule. It uses normal respiratory flow to capture particles by impaction. This article describes and evaluates the individual nasal air sampler.

The device performed well in laboratory experiments. In field trials, human subjects were able to wear the nasal air sampler comfortably for up to 4 hours, long enough to gather a representative sampling of allergens under most circumstances. Collection efficiency values ranged from about 50% for 5.0 µm particles, up to 100% for particles measuring 7.58 and 12.0 µm. The device has been tested successfully at airflow rates of 300

L/min. Technical details of materials and manufacturing are still being worked out, including improved adhesives for particle capture.

This nasal sampling device has the potential to measure a patient's true exposure to aeroallergens in the environment. In diagnostic use, the collected aerosols could be immunostained for identification of allergen particles using image analysis techniques. The current particle cutoff size is 5.0 µm at a mean flow rate of 25 L/min.

COMMENT: Allergists rely on environmental assessments and knowledge of airborne materials to determine relevant allergens in assessing respiratory disease. Unfortunately, this knowledge is usually based upon community rather than individual surveys, eg, pollen counting on a rooftop. The development of a practical, inexpensive nasal sampling device offers the potential for more specific diagnosis and treatment. This article describes such a device, although its performance is not acceptable with particles less than 5.0 µm, a size of some mold spores. Nevertheless, this device is a significant improvement over alternative, pump-driven personal samplers. Maybe the equivalent of a home visit by the allergist will be practical using such a device.

D. K. L.

Graham JAH, Pavlicek PK, Sercombe JK, et al: The nasal air sampler: a device for sampling inhaled aeroallergens.

Ann Allergy Asthma Immunol 84:599-604, 2000. ♦♦

Is Inhaled Nitric Oxide Effective in Status Asthmaticus?

THE selective pulmonary vasodilator nitric oxide (NO) also has significant bronchodilating effects. This led the investigators to try inhaled NO in 5 children with status asthmaticus. The first case was an 8-year-old admitted to the pediatric ICU with worsening respiratory distress. The patient had a respiratory rate of 60 breaths/min, cyanosis, chest retractions, poor breath sounds, and diffuse wheezing. Despite maximal medical therapy and intubation, the patient showed no improvement. At 5 hours after ICU admission, when the PaCO₂ was 138 mm Hg, the patient was started on inhaled NO, titrated from 10 to 20, 40, 60, and 80 ppm at 10-minute intervals. The child's ventilation and oxygenation improved rapidly, allowing discontinuation of NO after 18.5 hours. The patient was extubated the next day.

After this experience, the investigators administered inhaled NO to 4 consecutive children with life-threatening status asthmaticus that did not respond to other treatments. In 4 of these patients, NO led to rapid improvement in ventilation. Overall, 4 of the 5 children had a reduction in PaCO₂ of greater than 20%. There were no problems with systemic hypotension; methemoglobin level peaked at 1.95. All but 1 of the children survived to hospital discharge.

This experience suggests that NO is a safe and possibly effective treatment for children with status asthmaticus. The mechanism of its effect is unclear, >>

but may involve the bronchodilator and/or direct vascular effects of NO. Further study is needed to define the treatment role of NO in status asthmaticus, including patient factors predicting a response to therapy.

COMMENT: Based on its potential bronchodilator effects, inhaled NO produced rapid improvement in ventilation in 4 of 5 children with life-threatening asthma who had not responded to maximal conventional therapy. Further study is required to determine the role of inhaled NO in the treatment of status asthmaticus and, more importantly, the parameters that will identify patients most likely to respond.

J. B.-M.

Nakagawa TA, Johnston SJ, Falkos SA, et al: Life-threatening status asthmaticus treated with inhaled nitric oxide. *J Pediatr* 137:119-122, 2000. ♦♦

REVIEWS OF NOTE

Shrewsbury S, Pyke S, Britton M: Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ* 320:1368-1373, 2000.

COMMENT: Use of combination therapy in the treatment of patients with moderate and severe persistent asthma is becoming more and more commonplace. This meta-analysis clearly documents numerous advantages in clinical control of asthma by adding a long-acting bronchodilator instead of increasing the dose of inhaled corticosteroids. Importantly, the data do not suggest tolerance of increased exacerbations with combination therapy. The longest study reviewed was 26 weeks in duration; further long-term studies need to be performed.

M. S. B.

Delves PJ, Roitt IM: The immune system: first of two parts. *N Engl J Med* 343:37-49, 2000.

Delves PJ, Roitt IM: The immune system: second of two parts. *N Engl J Med* 343:108-117, 2000.

COMMENT: It is thought that a black hole is the most highly concentrated matter in the universe. Challenging that distinction is this pithy, highly organized, 22-page explication of the complexities of the immune system. The authors take us through the categories of immune defense, the cellular and molecular events of immune responses, and technologies for further studies. One suggestion: don't start underlining the important sentences—they all are. This is a fantastic review.

R. J. M.

American College of Allergy, Asthma & Immunology

85 West Algonquin Road, Suite 550
Arlington Heights, IL 60005-4425

BULK RATE
US POSTAGE
PAID
PERMIT NO 4453
ATLANTA, GA