AllergyWatch®

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

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Anti-IgE Antibody Is an Effective Treatment for Allergic Asthma

THE pathogenesis of allergic asthma involves IgE-mediated immune responses. Previous reports have described a recombinant humanized monoclonal antibody (rhuMAb-E25) that forms complexes with free IgE, thus blocking IgE interactions with mast cells and basophils. rhuMAb-E25 has been shown to reduce serum free IgE and reduce reactions to inhaled allergen. This anti-IgE antibody was studied for use in the treatment of allergic asthma.

Three hundred seventeen patients with allergic asthma were randomized to receive rhuMAb-E25 in an IV dose of 5.8 or 2.5 μg/kg/ng/IgE/mL, or placebo. With the first dose of rhuMAb-E25, serum free IgE dropped significantly: from 1,000 to 7 ng/mL in the high-dose group and from 1,060 to 14 ng/mL in the low dose group. Mean asthma symptom score decreased from 4.0 to 2.8 in both rhuMAb-E25 groups; use of β-agonist medications decreased as well. Among patients who initially required oral corticosteroids, median prednisone dosage decreased by 50% in the high-dose group and 65% in the low-dose group. All three groups received care that met current recommendations for asthma treatment, and significant improvement occurred in the placebo group as well. However, the rhuMAb-E25 groups showed greater symptomatic improvement, with similar rates of adverse events.

This randomized trial demonstrates the clinical efficacy of rhuMAb-E25 against allergic asthma, perhaps through its effects on the pathogenesis of the allergic response. The treatment is well tolerated; because of protein engineering, there are no immunogenic effects. This anti-IgE antibody is a promising treatment for moderate to severe allergic asthma.

COMMENT: *Asthma has a complex pathophysiology, and not all asthma is the result of the same mediator mix. IgE antibodies are certainly relevant to allergic diseases and asthma, so reducing IgE antibody* ➤➤

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

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- 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
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- American Journal of Medicine
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levels ought to assist asthma control. This study employed a humanized monoclonal anti-IgE intravenously for 20 weeks and demonstrated a most impressive drop in circulating IgE levels, and a less impressive but significant decline in asthma symptoms and steroid therapy. Drawbacks include IV administration and probable high cost for an ill-defined period.
R. J. M.
Milgrom H, Fick RB Jr, Su JQ, et al: Treatment of allergic asthma with monoclonal anti-IgE antibody. **N Engl J Med** 341:1966-1973, 1999. ♦♦

Study Shows Efficacy of Interleukin-4 Receptor for Atopic Asthma

INTERLEUKIN-4 (IL-4) plays an important proinflammatory role in asthma through several mechanisms, including stimulation of Th2 lymphocytes, which leads to production of IL-5, IL-13, and more IL-4. When IL-4 is absent, Th2 lymphocyte differentiation is inhibited, and secretion of these cytokines is reduced. This study evaluated the use of soluble recombinant human Il-4 receptor (IL-4R) as a treatment for atopic asthma.

The placebo-controlled trial included 25 patients with moderate atopic asthma, all requiring once-daily inhaled corticosteroids. They were randomized to receive IL-4R in a single nebulized dose of 500 or 1,500 μg, or placebo. The patients discontinued inhaled corticosteroids the day before the study drug was given.

There were no serious adverse effects of IL-4R. Serum levels of soluble IL-4R increased significantly from baseline. The high-dose IL-4R group showed significant improvement in FEV_1 on the fourth day after treatment. Asthma symptom score and β_2-agonist use were significantly reduced in patients taking the 1,500 μg dose of IL-4R. Possible differences in airway reactivity between groups could not be assessed.

The study documents the safety and efficacy of IL-4R given via nebulizer for the treatment of asthma. Although the study included patients with allergic asthma, IL-4R should be just as effective in patients with nonallergic asthma. There are potential concerns about the possible immune effects of long-term IL-4 blockade.

COMMENT: *Administration of the soluble extracellular portion of the high-affinity receptor for the proinflammatory cytokine IL-4 is shown to be safe and effective in the treatment of atopic patients with moderately severe asthma. A particularly attractive aspect of this novel treatment is the duration of effect, which may allow for treatment intervals of once a week or longer.*
J. R. B.
Borish LC, Nelson HS, Lanz MJ, et al: Interleukin-4 receptor in moderate atopic asthma: a phase I/II randomized, placebo-controlled trial.
Am J Respir Crit Care Med 160:1816-1823, 1999. ♦♦

Itraconazole Is Beneficial in Allergic Aspergillosis

THE long-term treatment for chronic allergic bronchopulmonary aspergillosis (ABPA)—a rare cause of asthma—is unclear. Previous studies of antifungal agents given to combat the *Aspergillus* organisms colonizing the bronchial tree have shown no improvement. The response to itraconazole in 14 asthmatic patients with ABPA was evaluated. All patients received oral itraconazole, 200 mg/d, for at least 1 year. The clinical, biologic, and functional findings were compared with those of a 2-year reference period before the start of itraconazole therapy. During the reference period, all patients were using inhaled corticosteroids, and 12 were taking oral glucocorticoids. All patients had a positive skin reaction to *A. fumigatus*, and 10 had an elevated serum IgE level. ➤➤

During the year of itraconazole treatment, the patients had significant clinical improvement. Mean FEV_1 improved from 1,433 to 1,785 mL/s. Blood eosinophil count, serum total IgE level, and serum precipitating antibodies against *A. fumigatus* all decreased. Oral glucocorticoid dosage was successfully lowered in all patients.

The antifungal agent itraconazole appears to be an effective treatment for ABPA. It significantly improves symptoms and pulmonary function while reducing or eliminating the need for oral glucocorticoids. Although the study notes a reduction in total IgE levels, there is no effect against specific IgE antibodies against *A. fumigatus*.

COMMENT: *This uncontrolled study adds to the evidence that itraconazole may have a role in the treatment of ABPA. Unlike previous studies, these authors reported pulmonary function data and showed impressive improvements in FEV_1. Prospective, controlled studies are needed to confirm the utility of itraconazole for ABPA.*
S. A. T.

Salez F, Brichet A, Desurmont S, et al: Effects of itraconazole therapy in allergic bronchopulmonary aspergillosis. **Chest** 116:1665-1668, 1999. ♦♦

Study Shows Allergic Cross-Reactivity Between Fish Species

THERE are unanswered questions about certain aspects of fish allergy. Previous studies have given conflicting results as to whether there is cross-reactivity among different species of fish; patients with fish allergy are generally advised to avoid all species of fish. To address the question of cross-reactivity, double-blind, placebo-controlled food challenges were performed in 9 adult patients with a history of fish allergy. The fish species tested were catfish, codfish, and snapper.

Seventy-four percent of fish challenges induced an objective reaction indicating an IgE-mediated response. The most frequent sign was emesis, occurring in 37% of challenges. Oral allergy syndrome was the most frequent subjective response, occurring in 84% of challenges. About three-fourths of the positive challenges were associated with significant levels of serum fish-specific IgE.

The findings suggest that distinct fish species have substantial levels of allergic cross-reactivity. Patients with a history of fish allergy are best advised to avoid eating all types of fish except those proven safe by a provocative challenge. The results also indicate that measurement of fish IgE antibodies may provide useful information for the diagnosis of fish allergy. However, double-blind, placebo-controlled food challenges will continue to be the most accurate technique.

COMMENT: *Allergists have long cautioned their fish-allergic patients to avoid all types of fish for a variety of reasons, including poor memory of the type of fish initially incriminated as an allergen as well as suspicions of cross-reactivity. Most allergists have fish-allergic patients who already know which kinds of fish they can and cannot eat. This study reinforces our belief that there can be extensive cross-reactivity between different fish families. The ubiquitous and early presence of oral allergy syndrome is noted—as well as a seeming paucity of lower respiratory reactions. Is fish less "asthmogenic" than, say, peanut allergen and more prone to affect the GI tract? Regardless, it is prudent to continue to advise our patients to avoid all types of fish if there is a history of an allergic reaction.*
S. R. W.

Helbling A, Haydel R Jr, McCant ML, et al: Fish allergy: is cross-reactivity among fish species relevant? Double-blind placebo-controlled food challenge studies of fish allergic adults. **Ann Allergy Asthma Immunol** 83:517-523, 1999. ♦♦

Psychiatric Side Effects of Steroids Are Common

SINCE the clinical introduction of corticosteroids, reports of psychiatric effects of steroid therapy have appeared in the literature. Many of these reports describe mood disorders, such as depression with suicidal ideation or mood lability. Others address mania or hypomania and even psychosis, with hallucinations and delusions. A large, retrospective study of psychiatric symptoms associated with corticosteroid therapy reported a 2% rate of mental disturbances. Another study, which included a semistructured interview, found a 26% rate of mania and a 10% rate of depression. Cognitive side effects of steroid use are also reported, including delirium. However, specific deficits in declarative memory—related to hippocampal function—are more common.

When psychiatric symptoms occur, they usually develop within the first 2 weeks of steroid therapy. They may be dose related. Psychiatric symptoms may also develop during corticosteroid withdrawal, or as a result of corticosteroid abuse or dependence. Most psychiatric symptoms resolve when corticosteroid therapy is discontinued. When this is not possible, lithium or antipsychotic therapy may be helpful. Tricyclic antidepressants may cause steroid-related psychiatric symptoms to worsen.

This paper reviews available data on the potential psychiatric side effects of corticosteroid therapy. Physicians should be alert for the occurrence of psychiatric and cognitive side effects in patients taking these widely used medications.

COMMENT: *Unfortunately, allergists frequently need to use systemic steroids to prevent the complications of allergic and other inflammatory disorders. This well-written review outlines the potential psychiatric complications of systemic steroid use. The authors review 50 years of data and conclude that psychiatric side effects are frequently dose-related and occur within the first 2 weeks of therapy.*
A. M.

Brown ES, Khan DA, Nejtek VA: The psychiatric ➤➤

side effects of corticosteroids. **Ann Allergy Asthma Immunol** 83:495-504, 1999. ♦♦

Diesel Exhaust Promotes Sensitization to Neoantigen

MANY recent studies have focused on the potential contribution of environmental diesel exhaust particles (DEPs) to exacerbation of allergic inflammation. In one study, exposure to DEPs plus another antigen led to increased IgE levels specific to that antigen, with a shift toward a Th2-like cytokine pattern. The ability of DEP exposure to cause primary sensitization to a neoantigen was studied using keyhole limpet hemocyanin (KLH), a glycoprotein isolated from mollusks that has no known cross-reacting antibodies in humans. Ten subjects with atopy received an initial nasal challenge with KLH, 1 mg, followed by two biweekly challenges with KLH, 100 µg. The same KLH immunization protocol was then followed in 15 additional atopic subjects. In the latter group, each subject received a DEP challenge 24 hours before KLH exposure. Nasal fluid samples were assessed for levels of KLH antibodies and cytokines.

Nasal fluid samples from subjects exposed to KLH alone showed IgG and IgA anti-KLH antibodies, but no IgE antibodies. However, specific IgE antibodies against KLH did appear in 60% of subjects exposed to DEPs followed by KLH. Levels of interleukin-4 in nasal fluid were significantly increased after challenge with DEPs and KLH, but not with KLH alone.

Exposure to DEPs plus a neoantigen appears to promote mucosal sensitization to that neoantigen, which does not produce sensitization on its own. Thus DEPs may drive primary sensitization to inhaled allergens. Diesel exhaust particles may act to promote sensitization by increasing secretion of interleukin-4 or by enhancing the ability of macrophages to function as antigen-presenting cells.

COMMENT: *The team of Bud Abbott and Lou Costello was greater than the sum of its parts: Abbott was the "adjuvant" for Costello's humor. What does this have to do with immunology? Have you ever heard of the neoantigen "keyhole-limpet hemocyanin" (KLH)? Put some in your nose and nothing happens, but first put in some diesel exhaust particles, followed by the KLH, and you'll probably develop an allergic sensitization with a Th2 pattern. This compelling study forces us to reconsider the impact of pollution on allergic disease.*
R. J. M.
Diaz-Sanchez D, Garcia MP, Wang M, et al: Nasal challenge with diesel exhaust particles can induce sensitization to a neoallergen in the human mucosa.
J Allergy Clin Immunol 104:1183-1188, 1999. ♦♦

Is Bee-Sting Allergy a Risk Factor for Paclitaxel Hypersensitivity?

HYPERSENSITIVITY reactions to paclitaxel are common, the result of IgE and other vasoactive substances stimulated by the drug. Based on clinical observations, the authors suspected that patients with reactions to paclitaxel had a high rate of bee-sting allergy. They tested this observation in a retrospective case-control study, including 19 patients with a history of anaphylactic reaction to paclitaxel and 38 controls.

Seven of the 19 patients with reactions to paclitaxel had a history of bee-sting allergy, compared with none of the controls. Animal allergies were also more frequent among the cases. Other plant and drug allergies were no different between groups.

Patients with bee-sting allergy may be predisposed to hypersensitivity reactions to paclitaxel. Such reactions can have high economic costs, in addition to psychologic trauma to the patient. Patients should be queried about allergy history before paclitaxel treatment. Those with a history of allergy—particularly bee-sting allergy—should receive a test dose of paclitaxel. Those who react to the test dose should be premedicated with oral dexamethasone for 48 to 72 hours.

COMMENT: *Adverse hypersensitivity reactions to paclitaxel occur in 2% to 8% of patients receiving the drug. This case-controlled chart review of 19 patients with documented anaphylactic reactions and 38 controls revealed a significant difference relating to the presence of hymenoptera sensitivity and animal allergy. There was no significant difference for plant or drug allergies. The authors recommend a complete allergy history before treatment with this drug and a test dose for those with a history of allergy—especially sensitivity to hymenoptera venom.*
E. J. B.
Grosen E, Siitari E, Larrison E, et al: Paclitaxel hypersensitivity reactions related to bee-sting allergy.
Lancet 354:288-289, 2000. ♦♦

Oral Montelukast Prevents Exercise-Induced Bronchoconstriction

EXERCISE can be a potent inducer of bronchoconstriction. Inhaled salmeterol can prevent exercise-induced bronchoconstriction (EIB), but tolerance is a potential problem. The leukotriene receptor antagonist montelukast was studied as a once-daily, oral agent for prevention of EIB. The randomized, double-blind trial included 191 patients with chronic asthma and at least a 20% decrease in FEV_1 in response to standardized exercise challenge. They were randomized to receive oral montelukast, 10 mg taken once in the evening, or inhaled salmeterol, 50 µg (2 puffs) taken twice daily. Most patients in both groups reported moderate to severe limitation of physical activity within the past month; 12% to 14% were using oral corticosteroids. Responses to treadmill exercise tests at day 1 to 3, week 4, and week 8 were compared between groups. For both medications, the exercise trials were performed around the trough of the dosing intervals.

Both treatments produced similar and significant reductions in maximal percentage decrease in FEV_1 in response to the first exercise test. The improvement was better sustained with montelukast: the percentage inhibition of the maximal percentage decrease in FEV_1 at week 8 was 57% with montelukast vs 33% with ➤➤

salmeterol. The slope of the maximal percentage decrease in FEV1 was -0.02%/d with montelukast vs 0.06%/d with salmeterol. At the end of the study, 67% of the montelukast group and 46% of the salmeterol group had less than a 20% maximal percentage decrease in FEV_1.

Both treatments were well tolerated, with adverse clinical events developing in about 40% of each group. The most common events were upper respiratory infections, headache, and asthma.

Over 4 to 8 weeks of therapy, oral montelukast provides better inhibition of EIB than inhaled salmeterol. The bronchoprotective effect of montelukast remains stable, whereas the effect of salmeterol decreases significantly over the weeks of treatment. Neither agent provides complete protection against EIB, however. The study was funded by Merck & Co., Inc.

COMMENT: *This multicenter trial addresses an important clinical question but raises many other questions. While it appears that montelukast is safe and effective in the treatment of EIB, it is not clear from this study if there is preferential benefit in patients with more severe disease or in those maintained on inhaled corticosteroids compared with salmeterol. The study measured response to exercise an average of over 9 hours after inhaled salmeterol. Would the same effects be seen if the exercise challenges were done at 2 hours following the dose? While this and other studies have noted a small loss of bronchoprotective effect of salmeterol over 8 weeks, they do not address the clinical significance of these changes. Both drugs are very useful medications whose roles continue to be defined.*
A. M.

Edelman JM, Turpin JA, Bronsky EA, et al: Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction: a randomized, double-blind trial. **Ann Intern Med** 132:97-104, 2000. ♦♦

Childhood Risk Factors for Reduced FEV_1 in Adulthood Studied

THERE are few data on the long-term outcomes of childhood asthma. Most studies of the effects of aging on lung function have focused on patients with chronic obstructive pulmonary disease or the general population. A 30-year follow-up study was performed to identify childhood factors associated with the level of FEV_1 in early adulthood.

The study included 119 patients with asthma who were 5 to 14 years old when first studied in 1966-69. Of these, 101 were re-examined at age 22 to 32, and again at age 32 to 42. Each examination included a physical examination; measurement of serum total IgE and peripheral blood eosinophils; skin testing; lung function testing; and a histamine challenge test.

At follow-up visits, more than 50% of subjects were former or current smokers. In multivariate analyses, subjects who had bronchial hyperresponsiveness and a low level of lung function as children were more likely to have a low level of FEV_1 in adulthood. From the second to the third follow-up examination, subjects who quit smoking and those continued to use inhaled corticosteroids had a lesser reduction in FEV_1.

Asthmatic children with reduced lung function and more severe hyperresponsiveness may be targeted for early intervention to improve their final prognosis, the results suggest. Young adults with asthma can slow their rate of decline in FEV_1 by quitting smoking and continuing to use inhaled corticosteroids. Efforts to prevent or delay asthma-related declines in lung function should include interventions in both early childhood and early adulthood.

COMMENT: *It is somewhat disconcerting that 59% of the asthmatics aged 32 to 42 in this study were current or former smokers. Not surprisingly, cessation of smoking has lessened the decline in lung function with aging. The association between consistent use of inhaled corticosteroids and a smaller decline in lung function in adulthood suggests that these agents will improve long-term outcomes in addition to providing short-term symptom control. This 30-year study related to the beneficial effects of inhaled steroids is truly unique.*
J. R. B.

Grol MH, Gerritsen J, Vonk JM, et al: Risk factors for growth and decline of lung function in asthmatic individuals up to age 42 years: a 30-year follow-up study. **Am J Respir Crit Care Med** 160:1830-1837, 1999. ♦♦

Salmeterol Shows Sustained Effect Over 1 Year of Treatment

THE long-acting β_2-agonist salmeterol can achieve good symptomatic control of asthma with twice-daily treatment. However, there is continued debate as to whether any sort of β_2-agonist should be given on a scheduled basis, in contrast to short-acting β_2-agonists on an as-needed basis. Persistence of effect and development of tolerance are potential concerns with β_2-agonists. This multicenter, randomized trial assessed the efficacy of salmeterol over a 1-year period, compared with placebo.

The study included 352 patients with mild to moderate asthma. One group received 52 weeks of treatment with salmeterol, 50 µg bid, and the other received placebo. Both groups were provided with albuterol rescue therapy, as needed. Males and females were equally represented, with an age range of 12 to 67 years. Mean percent predicted FEV_1 was 79% in both groups. Bronchial responsiveness to methacholine was assessed before, during, and after treatment.

Serial 12-hour spirometry data and patient diaries suggested significantly better asthma control with twice-daily salmeterol than with placebo. The bronchodilator properties of salmeterol were well maintained over the year of treatment. During treatment, bronchial responsiveness to methacholine was reduced to a modest extent. There was no significant increase in airway responsiveness after salmeterol was discontinued.

Salmeterol given in regularly scheduled doses provides better control of asthma than as-needed ➤➤

albuterol. Long-term use of salmeterol does not appear to be associated with deterioration in asthma control, as demonstrated with fenoterol.

COMMENT: *A major question in the use of long-acting beta agonists has been the concern over tolerance to the medication with long-term use, as well as increased bronchial hyperreactivity on discontinuation. Kemp et al. addressed both of these issues in a 52-week study of salmeterol in patients with mild to moderate asthma. This agent showed continued bronchodilation throughout the study year, with no evidence of increased bronchial reactivity 7 days after treatment by methacholine challenge. These results are reassuring with the increased use of combination therapy consisting of inhaled corticosteroids and long-acting beta agonists in patients with moderate to severe persistent asthma.*
M. S. B.
Kemp JP, DeGraff AC, Pearlman DS, et al: A 1-year study of salmeterol powder on pulmonary function and hyperresponsiveness to methacholine.
J Allergy Clin Immunol 104:1189-1197, 1999. ♦♦

Vocal Cord Dysfunction: a Common Cause of Exertional Dyspnea

PATIENTS with vocal cord dysfunction (VCD) have paradoxical closure of the vocal cords during inspiration. The resulting limitation of airflow causes often-dramatic symptoms such as wheezing, stridor, and dyspnea on exertion, leading to an incorrect diagnosis of asthma. A prospective study of 40 patients with VCD, including laryngoscopy and pulmonary function testing, is reported.

The subjects with VCD were active-duty military personnel who developed exertional dyspnea during physical training. Most had received treatment for a presumptive diagnosis of exercise-induced asthma. All patients underwent flexible laryngoscopy, performed before and after exercise, to assess the occurrence of vocal cord adduction during inspiration. Pulmonary function tests and bronchoprovocation studies were performed as well. Twelve asymptomatic active-duty personnel were studied as controls.

Laryngoscopy demonstrated the presence of VCD in 15% of the subjects with exertional dyspnea, compared with none of the controls. Pulmonary function results were similar for patients with exertional dyspnea with and without VCD. Sixty percent of patients with VCD had a positive response to methacholine challenge, compared with 29% of the VCD-negative patients with dyspnea and 16% of the asymptomatic controls. Patients with VCD and a positive methacholine challenge test were more likely to have a significant decrease in FEV_1/FVC, apparently because of reduced inspiratory volume.

This study suggests that VCD is common in young patients with exertional dyspnea. This possibility should be considered especially in patients who have no response to treatment for asthma or exercise-induced asthma. Methacholine bronchoprovocation studies may provide useful information, but direct observation of paradoxical inspiratory vocal cord closure during inspiration is the gold standard for diagnosis.

COMMENT: *Vocal cord dysfunction is an asthma masquerader well known to most allergists, yet its epidemiology is completely unknown. In this study, 15% of active military subjects who failed their physical training due to exertional dyspnea were diagnosed with VCD by laryngoscopy. Sixty percent of the subjects with VCD had a positive methacholine challenge, though the authors argue that the response to methacholine may not have been intrathoracic airflow obstruction since the change in FEV_1/FVC was modest.*
S. A. T.
Morris MJ, Deal LE, Bean DR, et al: Vocal cord dysfunction in patients with exertional dyspnea.
Chest 116:1676-1682, 1999. ♦♦

Churg-Strauss Syndrome Can Occur Without Leukotriene Receptor Antagonists

PREVIOUS studies have suggested that Churg-Strauss syndrome (CSS)—a syndrome characterized by pulmonary and systemic vasculitis, extravascular granulomas, and hypereosinophilia—is a possible complication of leukotriene receptor antagonist therapy. Seven cases of complete or incomplete CSS occurring in asthma patients who were not taking leukotriene modifiers are reported. There were 4 women and 3 men, mean age 59 years. Six met American College of Rheumatology criteria for CSS. All had asthma and sinus disease. Treatment included inhaled corticosteroids in all patients, but none were taking leukotriene receptor antagonists.

Signs of CSS usually developed as the patients' dose of systemic corticosteroids was being tapered or discontinued. However, 3 of the patients were not taking oral corticosteroids at the time CSS occurred. Three patients were positive for antineutrophil cytoplasmic antibodies, and 4 had histologically confirmed vasculitis. High-dose corticosteroids yielded a response in 5 of the 7 patients.

This experience demonstrates that CSS can occur in asthma patients even if they are not taking leukotriene receptor antagonists. The characteristics of these patients are similar to those previously reported as developing zafirlukast-associated CSS. Steroids may mask signs of CSS, which can occur even in patients with nonsevere asthma of short duration who are taking inhaled steroids only.

COMMENT: *To date, leukotriene receptor antagonists have had minimal side effects except for the reports of patients on these agents who developed Churg-Strauss syndrome, usually after tapering or decreasing corticosteroid therapy. Bili et al. describe 7 patients who developed manifestations of CSS while tapering oral or inhaled corticosteroids, even though they had never received a leukotriene receptor antagonist. Clinicians should be aware of the possibility of CSS in all asthmatic patients.*
M. S. B.
Bili A, Condemi JJ, Bottone SM, Ryan CK: Seven cases of complete and incomplete forms of Churg- ➤➤

Strauss syndrome not related to leukotriene receptor antagonists. **J Allergy Clin Immunol** 104:1060-1065, 1999. ♦♦

High Tryptase Levels Cannot Account for SIDS

RESEARCH has identified several risk factors for sudden infant death syndrome (SIDS), including maternal smoking and prone sleeping position. The hypothesis that allergy may be involved was supported by the finding of elevated tryptase concentrations in infants who died of SIDS. To clarify this relationship, the factors potentially associated with elevated mast cell tryptase levels were studied in 44 infants who died of SIDS.

Postmortem serum samples were obtained for measurement of mast cell tryptase and total IgE. Potential allergens—including food allergens, Phadiatop, and latex—were evaluated in radioallergosorbent tests (RAST). Radial immunodiffusion was performed to measure IgG subclasses, IgM, and complement factors. In addition, mast cells from the lungs and heart were studied by immunohistochemistry using antitryptase antibodies.

Serum mast cell tryptase levels were elevated—greater than 10 µg/L—in 40% of subjects. Thirty-three percent had elevated total serum IgE, although this finding was unrelated to the mast cell tryptase level. When total IgE was elevated, IgG1 and IgG2 were elevated as well. The IgE level was higher for infants who died in the spring. Three subjects had positive RAST results, all of whom had elevated total IgE. Only 1 subject with food allergy had evidence of an allergic reaction around the time of death. Six subjects had very high tryptase values of greater than 20 µg/L, but all were negative on RAST.

These findings do not support the hypothesis that SIDS deaths are related to allergy. Instead, they suggest the presence of non-IgE-related mast cell degranulation, possibly resulting from hypoxia related to prone positioning or a postmortem artefact.

COMMENT: *The observation that sudden infant death is often associated with elevated serum mast cell tryptase has led us to focus on anaphylactic or anaphylactoid reactions as a cause. This study confirms the mast cell tryptase association in SIDS. However, extensive serologic testing failed to identify evidence to support an allergic cause in 43 of the 44 cases. There was an association between tryptase levels and a prone body position at death, prompting the authors to speculate that the tryptase may be due to hypoxia. S. A. T.*

Edston E, Gidlund E, Wickman M, et al: Increased mast cell tryptase in sudden infant death—anaphylaxis, hypoxia, or artefact? **Clin Exp Allergy** 29:1648-1654, 1999. ♦♦

Bronchial Hyperresponsiveness Persists in Asymptomatic Children With Asthma

IT has been reported that about one-third of children with asthma are still symptomatic in young adulthood. However, previous studies of asthma persistence have not included airway hyperresponsiveness (AHR) testing. Thus the relationship between AHR and persistent asthma symptoms is unclear. As part of a large follow-up study of the natural history of childhood asthma, the relationship between AHR and asthma symptom status was assessed.

The study cohort included 457 children with asthma living in Montreal. All received a pediatrician's diagnosis of asthma at the age of 3 or 4 years. The parents of all children provided information on respiratory symptoms and medication use during the subsequent 6 years. Spirometry and methacholine challenge studies were performed in a sample of 88 children who had had an episode of wheezing during the follow-up period.

Twenty-two percent of the children were asymptomatic when AHR testing was performed. Another 29% were having symptoms, but receiving no medications. The remaining 49% of patients were symptomatic and receiving medication, including 31% who were receiving anti-inflammatory medications. Testing revealed significant AHR in all except 2 of the children. Three-fourths of patients who were symptomatic but not receiving medication had greatly enhanced AHR, with a PC_{20} of less than 2 mg/mL.

Almost all young children diagnosed as having asthma still have AHR when followed up 6 years later. Many of these children are reportedly asymptomatic, despite having PC_{20} values of less than 2 mg/mL. This finding may relate to several potential sources of error in parental responses to the study questionnaire. Furthermore, many children with this degree of AHR are not currently receiving treatment.

COMMENT: *This Montreal study is part of a large inception cohort study to investigate the natural history of asthma among 457 children. This section focused on a subset of asthmatic children who required emergency room evaluation at age 3 or 4 and had asthma symptoms at some point over the subsequent 6 years. Virtually all of the 9- and 10-year-olds had significant bronchial hyperresponsiveness, regardless of whether they had ongoing symptoms, yet 37% remain untreated. S. A. T.*

Gautrin D, Lapierre J-G, Malo J-L, Infante-Rivard C: Airway hyperresponsiveness and symptoms of asthma in a six-year follow-up study of childhood asthma. **Chest** 116:1659-1664, 1999. ♦♦

Measles May Be a Risk Factor for Allergy

IT has been suggested that the ongoing epidemic of asthma in the Western world may be related to reductions in communicable disease achieved through vaccination programs. This leads to the hypoth- ➤➤

esis that natural measles infection may reduce the risk of allergic disease. This hypothesis was evaluated using Finnish registry data on 547,910 children and adolescents receiving the measles-mumps-rubella vaccination. At that time, data on history of measles and allergic diseases—rhinitis, eczema, and asthma—were collected for each patient.

The 20,690 patients who had had measles had higher rates of allergic disease. The age-adjusted prevalence ratios were 1.32 for eczema, 1.41 for rhinitis, and 1.67 for asthma; all of these associations were significant. The link between measles and allergic disease crossed all age groups, urban vs rural area of residence, and number of contacts at home or in day care.

These population-based data suggest that children with measles are at increased risk of various allergic diseases. They do not support the hypothesis that natural measles infection lowers the risk of atopy. Although errors in the diagnosis of atopy are likely in this study, they are no more likely for children with vs those without a history of measles.

COMMENT: *This extremely large (greater than half a million children followed) study defies current theories that the reduction of natural measles infection because of vaccination may increase the risk of atopic disease. In the study, children with a history of measles actually had more allergic disease. The accompanying editorial reviews the "hygiene hypothesis," which states that repeated infections in early childhood (which might be seen in larger families) may prevent the Th1-Th2 imbalance seen in allergic disease. If this theory is true, are we then making a mistake to remove children from day care when they develop recurrent upper respiratory infections? Surely the infectious exposure in a large day care center would mimic, if not exceed, the exposure in a large family. Are we increasing or decreasing these children's chances of developing atopy?*
S. R. W.

Paunio M, Heinonen OP, Virtanen M, et al: Measles history and atopic diseases: a population-based cross-sectional study. **JAMA** 283:343-346, 2000. ♦♦

Inhaled Anticholinergics Are Cost-Effective for Acute Pediatric Asthma

PREVIOUS reports have suggested that giving anticholinergic agents along with β_2-agonists can improve lung function and prevent hospitalization for pediatric patients seen in the emergency department for severe acute asthma. One study claimed a 9% reduction in the risk of admission, but provided no data on the cost-effectiveness of this intervention.

A cost-effectiveness analysis suggested that the cost of giving anticholinergics would be only about £8 to avoid one hospital admission. Thus anticholinergic use would save an estimated £80 for each case of severe asthma treated. Extrapolated to the population of England—where about 7,200 children aged 5 to 15 are hospitalized from the emergency department with asthma each year—the estimated 5-year savings were £437,800.

The data support the cost-effectiveness of anticholinergic agents for children and adolescents seen in the emergency department for severe, acute asthma. This conclusion persists through a range of assumptions in the study model. Additional personal benefits can be expected to accrue as well.

COMMENT: *With changes in the health care environment, demonstrating cost-effectiveness of a medical treatment is becoming as important as showing its efficacy and safety. Inhaled anticholinergic agents have been shown to add to the bronchodilation of short-acting beta-agonists in children with acute, severe asthma treated in the emergency department. British researchers analyzing outcomes data on such children estimated that anticholinergic treatment would cost about $13 per admission avoided, which implied a net saving of $128 per severe case treated. These data further confirm the role of anticholinergics as a beneficial additive therapy for asthmatic children seen in the emergency department.*
M. S. B.

Lord J, Ducharme FM, Stamp RJ, et al: Cost effectiveness analysis of inhaled anticholinergics for acute childhood and adolescent asthma.
BMJ 319:1470-1471, 1999. ♦♦

Insect Sting Allergy Carries Psychologic Sequelae

ACUTE allergic reactions to insect stings can include widespread urticaria, cutaneous or laryngeal edema, bronchospasm, and loss of consciousness. Patients receiving immunotherapy after such systemic reactions are almost completely protected against future reactions. Yet clinical experience suggests that some patients perceive their allergy as a debilitating problem with a major impact on quality of life. A group of 97 patients receiving insect venom immunotherapy were studied to assess related psychologic distress. The study included a 12-item scale designed to assess debilitating beliefs. Ten items from the Impact of Event Scale were used to assess preoccupation with the systemic reaction.

Up to one-third of patients held debilitating beliefs, such as that they should always be under medical surveillance or that they should limit their work and recreational activities, including avoidance of open areas. Twelve percent were continuously preoccupied with their systemic reaction. Many patients reported moderate to severe impairment in quality of life and symptoms of emotional distress. The findings were unrelated to any patient characteristics, including whether the patients had reached their full maintenance dose.

Despite immunotherapy, many patients with a history of insect sting allergy experience significant adverse psychologic consequences. These patients may have debilitating beliefs about their allergy, which are associated with emotional distress, preoccupation with their systemic reaction, and restriction of their activities. Patients with systemic reactions to insect stings may benefit from interventions to correct their inaccurate debilitating beliefs. ➤➤

COMMENT: *As allergists, we prevent death by administering hymenoptera immunotherapy to appropriate patients. However, this study suggests that these patients often remain profoundly concerned about their risk. In addition to customary patient education, perhaps we should be prepared to address the more complicated emotional issues faced by some patients who have experienced anaphylaxis.*
S. A. T.
Confino-Cohen R, Melamed S, Goldberg A: Debilitating beliefs, emotional distress and quality of life in patients given immunotherapy for insect sting allergy. **Clin Exp Allergy** 29:1626-1631, 1999. ♦♦

New Developments in Allergy and Immunology Reviewed

THE last few years have seen significant developments in asthma research, as well as in other areas such as rhinitis and immunotherapy. Key findings in these and other areas of allergy and immunology are reviewed as part on a continuing update series.

Some recent studies have underscored the important effects of the indoor environment on asthmatic patients. One report indicated that patients with perennial asthma have sensitization to specific indoor allergens, as opposed to generalized IgE hyperresponsiveness. A study of urban children assessed dose-response relationships for current exposure to mite, cockroach, and cat allergens. Sensitization to cockroach allergen was most strongly associated with exposure in the bedroom. Another study suggested that children's exposure to cat allergen could be reduced by avoiding carpeting in day care centers and other settings where children spend a lot of time. A laboratory study showed that diesel exhaust particles influence synthesis of cytokines involved in IgE production.

Many important studies regarding asthma treatment have appeared recently. One study underscored the need for objective measurements of airway obstruction in assessing the results of treatment for chronic asthma. However, another warned that patients' compliance with the use of peak flow meters—which play a key role in measuring airflow obstruction—decreases significantly over time. Other reports discussed the underuse of drug treatments that could prevent emergency department visits for asthma and the inappropriate use of bronchodilators in the absence of anti-inflammatory drugs. The update cites several other recent asthma treatment studies reviewed in previous issues of *AllergyWatch*.

A study of patients with rhinitis demonstrated the quality-of-life benefits of using topical steroid sprays to reduce nasal congestion. An immunotherapy study suggested that more than 80% of patients with insect-sting anaphylaxis can safely discontinue venom immunotherapy after 5 to 6 years. However, the study identifies some groups of patients who remain at risk, and require continued immunotherapy.

COMMENT: *In this ongoing series of specialty updates in the* Annals of Internal Medicine, *the specialty of allergy is highlighted. This update reviews important areas such as asthma, rhinitis, and allergen immunotherapy. It serves as an excellent reference for specialists or primary care providers who seek up-to-date reviews for continuing education or preparing for a presentation.*
A. M.
O'Hollaren MT: Update in allergy and immunology. **Ann Intern Med** 132:219-226, 2000. ♦♦

Chest Involvement in Churg-Strauss Syndrome Studied

CHURG-Strauss syndrome (CSS) is a rare condition, nearly always occurring in patients with asthma or allergy, consisting of systemic vasculitis, extravascular granulomas, and eosinophilia. The major sites of involvement are the lungs, skin, and nervous system; biopsies of these sites are performed to confirm the diagnosis of CSS. The authors describe the clinical and radiologic findings of 9 patients with thoracic involvement with CSS.

The patients were 5 women and 4 men, median age 35 years. All had asthma, with an average disease duration of 28 months before the first symptoms of vasculitis and eosinophilia developed. The mean peak eosinophil count was 8,726/μL, with a mean differential count of 41%. Systemic vasculitis involving the lung was present in all 9 patients, along with 2 to 4 extrapulmonary organs. The vasculitic phase was associated with elevated IgE levels in 6 of 6 patients studied. The initial clinical manifestations included respiratory symptoms in 56% of patients, painful paresthesias in 44%, and erythematous skin nodules in 44%. Eight patients had a positive tissue biopsy.

Chest radiographic findings included bilateral nonsegmental consolidation, reticulonodular opacities, and bronchial wall-thickening. On thin-section CT, all patients showed bilateral ground-glass opacity, usually with centrilobar nodules within. Other CT findings included bronchial wall thickening, air space consolidation, and increased vessel caliber.

The study illustrates the variable chest manifestations of CSS. This diagnosis should be considered in any patient with asthma and hypereosinophilia who has CT findings such as bilateral subpleural consolidation with a lobular distribution and centrilobular nodules. The diagnosis is easier to make if associated skin or nervous system involvement is present.

COMMENT: *This review of Churg-Strauss syndrome involved a careful analysis of 4 men and 5 women with a history of asthma averaging 28 months before the initial manifestation of vasculitis and marked peripheral blood eosinophilia. Each of these patients had systemic vasculitis involving the lung and 2 to 4 extrapulmonary organs (most commonly the skin and nervous system). Unfortunately, no mention of drug therapy is made by the authors.*
E. J. B.
Choi YH, Im J-G, Han BK, et al: Thoracic manifestation of Churg-Strauss syndrome: radiologic and clinical findings. **Chest** 117:117-124, 2000. ♦♦

Study Identifies Risk Factors for Missed Medical Care by Teens

UNLESS adolescents at risk of health problems seek health care services, physicians have no opportunity to address those problems. Many different social and economic factors affect health care access and utilization by children and adults. This study assessed the frequency of missed health care by adolescents, and factors associated with such missed opportunities.

The cross-sectional analysis used interview data from 2,268 adolescents, collected as part of the National Longitudinal Study of Adolescent Health. Nineteen percent of responding adolescents reported at least one occasion during the previous year in which they thought they should receive health care services but did not. Adolescents who smoked were more likely to report missed care than those who did not. Other factors associated with missed health care included no insurance, not having had a physical examination within the past year, older age, minority race, single-parent family, disability, frequent alcohol use, and sexual intercourse. The most common reason for missed care was thinking the problem would go away on its own. Others included not being able to get a parent or guardian to go with them to the medical appointment and not wanting parents to know about the appointment.

Missed opportunities for health care are very common among adolescents. This may place adolescents at risk of health problems, especially since those who miss health care are more likely to engage in at-risk behaviors. Some of the reasons for missed health care have to do with the complex relationship between the parent and child during adolescence. Taking responsibility for one's own health is one of the developmental tasks of adolescence.

COMMENT: *These data taken from the National Longitudinal Study of Adolescent Health help explain why certain teenagers with asthma are at such high risk. Almost one-fifth of the study participants reported foregoing medical care at least one time in the past year. Behavioral issues such as smoking (a surrogate marker for rebelliousness, perhaps?) were significant, but factors outside the teenager's control were more numerous as potential reasons for missed opportunities to seek medical care. Uninsured and minority teens were more likely to forego care, but how sad to see such reasons as "had no transportation" or "parent or guardian would not go" on the list. Caring for adolescents will always be challenging, but the medical community must be ever-mindful that not all compliance issues are the teenager's fault.*
S. R. W.
Ford CA, Bearman PS, Moody J: Foregone health care among adolescents.
JAMA 282:2227-2234, 1999. ♦♦

Eotaxin Acts to Prime Eosinophils to Produce Reactive Oxygen Species

THE CC chemokines RANTES and eotaxin, which have chemotactic effects on eosinophils, are thought to be involved in allergic inflammation. However, there are few details on eotaxin's role in eosinophil activation. Cellular or tissue damage may be caused by reactive oxygen species (ROS) from eosinophils. This study used luminol- and lucigenin-dependent chemiluminescence to examine the effects of eotaxin on ROS from eosinophils, in comparison with those of RANTES and interleukin-5.

Eotaxin had a dose-dependent priming effect on the production of ROS by eosinophils. On luminol-dependent chemiluminescence, ROS from untreated eosinophils had a maximal intensity count value of 4,597, compared with 11,142 for ROS from eosinophils treated with a 10 nM concentration of eotaxin. The ROS-priming effect of eotaxin was stronger than that of other eosinophil-activating cytokines and chemokines. This effect was inhibited by pertussis toxins, which causes ADP-ribosylation of G proteins; by the phosphatidylinositol-3-kinase inhibitor wortmannin; and by the tyrosine kinase inhibitor genistein.

Eotaxin has a dose-dependent priming effect on eosinophil ROS. The priming effect of eotaxin is stronger than that of RANTES, which with it shares the CCR_3 receptor. After stimulation with eotaxin, the signal transduction process leading to eosinophil activation appears to involve pertussis toxin-sensitive G proteins, phosphatidylinositol-3-kinase, and tyrosine kinase. Eotaxin may affect the pathogenesis of allergic inflammation via its eosinophil-priming activity as well as its involvement in eosinophil chemotaxis.

COMMENT: *Eotaxin is a selective and potent chemotactant for eosinophils to local inflammatory sites. Eosinophils are activated by cytokines and adhesion molecules and are felt to injure epithelial cells resulting in airway hyperreactivity. This study demonstrated eotaxin's role in allergic inflammation by priming the eosinophil's oxidative metabolism as well as in selective eosinophil chemotaxis. A future therapeutic approach in asthma will involve eotaxin antagonists.*
E. J. B.
Honda K, Chihara J: Eosinophil activation by eotaxin—eotaxin primes the production of reactive oxygen species from eosinophils.
Allergy 54:1262-1269, 1999. ♦♦

One-Tenth of Adult Asthma Cases May Be Occupationally Related

ASTHMA is an increasingly common problem among working-age adults, and one that is potentially related to occupational exposures. Various approaches have been used to estimate the proportion of cases of asthma attributable to occupational causes. A 30-year literature review and synthesis was performed to come up with a reliable estimate of the attributable risk ➤➤

for occupational causes of asthma. In addition to performing a Medline search for the years 1966 to 1996, the authors sought recent abstracts of studies estimating the asthma risk for various occupations. Some studies estimated occupational attributable risk for asthma, while others included population-based data on the incidence of occupationally related asthma.

A total of 23 studies reported on the occupationally attributable risk of asthma, with estimates ranging from 2% to 33%. The median attributable risk was 9%, with a mean of 12%. Similar median risk estimates were obtained from studies of various types, including estimates derived from published data and those extrapolated from incidence data. Estimated incidences of occupational asthma varied widely among countries, from 1.2 to 17.4 per 100,000 person-years. The one study to differentiate between new-onset and reactivated occupational asthma suggested attributable risks of 26% and 19%, respectively.

The available data suggest that about 9% of cases of asthma in adult patients can be attributed to occupational factors. Because of publication bias, the true attributable risk may be even higher. The occupationally attributable risk of asthma may differ for new-onset and reactivated asthma, although the clinical implications of the two types are similar. The authors note that the heterogeneity of the data precluded a true meta-analysis.

COMMENT: *These authors reviewed and synthesized the literature between 1966 and mid-1999 in an attempt to reach a reliable estimate of adult asthma associated with workplace exposures. They conclude that occupational factors are associated with about 1 in 10 cases of adult asthma. However, they do not distinguish new-onset disease and reactivation or worsening of pre-existing asthma. Although the authors consider these scenarios "equally relevant" from a clinical perspective, they have markedly disparate repercussions in issues of compensation and therapeutic approach.*
E. J. B.
Blanc PD, Toren K: How much adult asthma can be attributed to occupational factors?
Am J Med 107:580-587, 1999. ♦♦

ISS-ODNs May Offer New Approach to Cedar Pollen Immunotherapy

GIVING immunostimulatory DNA sequence oligodeoxynucleotides (ISS-ODNs) along with protein antigens appears to be a promising approach to allergen-specific immunotherapy. The effects of adding ISS-ODN to cedar pollen protein allergens were studied in BALB/c mice. The allergens used were Cry j 1 and Cry j 2, which are major causes of allergic disease in Japan.

Injection with allergens and ISS-ODN resulted in increases in IgG2a titers and interferon-γ release in mice with either secondary or primary Th2 and IgE responses. Treatment with ISS-ODN also inhibited production of IgE antibody. In contrast, control animals receiving allergens and mutant ODN showed decreases in IgG1 titers and interleukin-4 release.

In this animal model, coadministration of cedar pollen allergen with ISS-ODN is associated with a shift from a Th1 to a Th2 immune response and inhibition of IgE antibody production. The use of ISS-ODN may offer a new approach to immunotherapy for cedar pollinosis. Other approaches under investigation included modifications of cedar pollen allergen T-cell epitopes and an orally administered dominant T cell-determinant peptide.

COMMENT: *One probable mechanism of conventional allergen immunotherapy is the shift of a Th2-predominant antigen response pattern to a Th1 type. These authors immunized mice with cedar pollen antigens coadministered with an immunostimulatory DNA sequence (oligonucleotide) and demonstrated an enhanced Th1 response and inhibition of IgE production. From these and other studies, one gets the impression that we are on the verge of a new era of immunotherapy.*
R. J. M.
Kohama Y, Akizuki O, Hagihara K, et al: Immunostimulatory oligodeoxynucleotide induces T_{H1} immune response and inhibition of IgE antibody production to cedar pollen allergens in mice.
J Allergy Clin Immunol 104:1231-1238, 1999. ♦♦

Gastroesophageal Reflux Provokes Nighttime Bronchoconstriction in Asthma Patients

ASTHMA patients have a high rate of gastroesophageal reflux (GER), treatment for which may lead to improvement in asthma symptoms. Nighttime episodes of reflux are a potential contributor to nocturnal asthma exacerbations, although this relationship remains controversial. The link between nocturnal GER and asthma was assessed in 7 adult patients with nonseasonal asthma and previously untreated moderate to severe GER. In the sleep laboratory, all patients underwent continuous, simultaneous monitoring of respiratory resistances and esophageal pH.

A total of 101 episodes of GER occurred during the study night. Of these, 72 lasted less than 5 minutes (median 1 minute) and 29 lasted longer than 5 minutes (median 9 minutes). The patients spent a median of 17% of the total study time with GER. Both short and long GER episodes were associated with significantly increased lower respiratory resistance measurements. However, longer episodes of reflux produced greater and longer-lasting episodes of bronchoconstriction: the lower respiratory resistance measurement 10 minutes after the end of the GER episode was significantly related to the duration of GER.

In adult asthma patients with GER, spontaneous episodes of acid reflex appear to be a significant factor in provoking and sustaining occurrences of nocturnal bronchoconstriction. The duration of the GER episodes has an important effect: pulmonary function is slower to recover after acid is cleared from the ➤➤

esophagus, and bronchial inflammation causes a delayed bronchodilator effect. However, some episodes of bronchoconstriction are unrelated to GER.

COMMENT: *This study uses a direct, continuous, and simultaneous evaluation of both respiratory resistances and intraesophageal pH during nighttime to demonstrate a significant role of spontaneous GER in provoking and sustaining nocturnal bronchoconstriction in adult asthmatics with moderate to severe GER.*
J. B.-M.
Cuttitta G, Cibella F, Visconti A, et al: Spontaneous gastroesophageal reflux and airway patency during the night in adult asthmatics.
Am J Respir Crit Care Med 161:177-181, 2000. ♦♦

Should Combined DTPa-Hib Conjugate Vaccines Be Used?

CONJUGATED *Haemophilus influenzae* type b (Hib) vaccines were introduced to overcome problems with poor immunogenicity in children younger than 18 months. Because Hib vaccine is given at the same time as diphtheria-tetanus-pertussis (DTP) vaccine, combination vaccines were developed. However, the combination of Hib conjugates with DTP vaccines containing acellular pertussis (DTPa) was associated with a reduced Hib antibody response.

This led to concerns over the efficacy of combined DTPa-Hib conjugate vaccines. Further study is needed to clarify the mechanisms of interaction between these vaccines. However, a review of the available data suggests that the interaction is not clinically important. The serologic indicators of efficacy used to evaluate Hib polysaccharide vaccines do not appear to apply to Hib conjugates. The authors' own studies suggest that reduced antibody responses do not lead to impaired function of the antibodies induced, or to impairment of immune memory against Hib. More recent DTPa-Hib conjugate combination vaccines show few signs of immune interference. These combinations have been extensively used in many European countries, with no increase in invasive Hib disease.

As long as surveillance efforts to detect clinical Hib disease are continued, the evidence supports the use of combined DTPa-Hib vaccines for primary immunization. As new vaccines for children are introduced, the need for combination vaccines will become more pressing. Combined vaccines offer key advantages—especially the need for fewer injections and office visits—which probably outweigh potential concerns about interactions and antibody titers.

COMMENT: *This review focuses on concerns related to the lower antibody response to Hib in DTP-Hib combination vaccine containing an acellular pertussis (Pa) component. The authors argue concerns are unwarranted since serologic correlates of efficacy previously applied for Hib polysaccharide vaccines are inappropriate for Hib conjugates. They encourage introduction of DTPa-Hib combinations to facilitate inclusion of Hib into a crowded childhood immunization schedule.*
E. J. B.
Eskola J, Ward J, Dagan R, et al: Combined vaccination of Haemophilus influenzae *type b conjugate and diphtheria-tetanus-pertussis containing acellular pertussis.* **Lancet** 354:2063-2068, 1999. ♦♦

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