Advances in pediatric and adult asthma

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Last year's review on adult and pediatric asthma highlighted reports related to asthma genetics, the importance of upper airway management, the costs of asthma, and the importance of early recognition and intervention. This year we will organize our discussion to review recent reports related to the origins and persistence of asthma in both adults and children. We highlight Journal publications from 2004, along with recent key publications from other medical journals, to provide a perspective on the rapidly developing areas of genetics, including pharmacogenetics, respiratory infection, biomarker measurements, and asthma pharmacotherapy. This new understanding of the pathogenesis of asthma combined with clinical applications of genetics and biomarkers should lead to new management strategies. Asthma management is likely to change in the coming years from a strategy directed to the best outcome in groups of patients to an individualized approach to assessment and management. (J Allergy Clin Immunol 2005;115:470-7.)

Key words: *Asthma, biomarkers, corticosteroids, genetics, immunomodulators, long-term control therapy*

In last year's review we highlighted reports related to asthma genetics, the need to control upper airways symptoms for asthma management, the pharmacoeconomics of asthma, and early recognition and intervention.[1] A National Heart, Lung, and Blood Institute Working Group recently identified priorities for asthma research, including immunology, asthma exacerbations, airway remodeling, genetics, therapeutics, and vascular features of asthma.[2,3] This year's review will focus on the origins and persistence of asthma as 2 broad categories of asthma pathogenesis (Fig 1).

Abbreviations used
ECP: Eosinophilic cationic protein
ICS: Inhaled corticosteroid
LT: Leukotriene
RSV: Respiratory syncytial virus

IMPACT OF ASTHMA

The international variations in the severity, control, and management of asthma were reported on by Rabe et al.[4] A substantial effect of asthma on loss of schooldays and workdays, a significant proportion of patients that continue to have symptoms and lifestyle restrictions, a high proportion of adults as current smokers, low use of preventive therapy (including those used in patients with severe asthma), and low use of objective lung function testing are noted worldwide.

Vargas et al[5] evaluated the characteristics of children at risk for asthma in a Head Start program. These young children with asthma had significant environmental tobacco smoke exposure, were highly atopic and symptomatic, and did not receive appropriate medication treatment. Becker et al[6] focused on asthma deaths in competitive athletes. Those who had fatal asthma exacerbations were usually white males between the ages of 10 and 20 years with mild intermittent or persistent asthma by history. Fatal asthma exacerbations occurred in both competitive and recreational athletes and could be precipitated by a sporting activity.

ORIGINS OF ASTHMA

Exploration of genetic origins is leading to a better understanding of phenotypic variation, which in turn might yield a more individualized approach for medication selection. Openshaw et al[7] recently categorized the influences on asthma origins as genetic, environmental, and age-related or developmental.

Genetics

The genetic influences on asthma are described in several recent reviews.[8,9] Our discussion addresses pharmacogenetics and gene-environmental interactions.

Pharmacogenetics. Pharmacogenetics examines genetic variability of response to medications, such as

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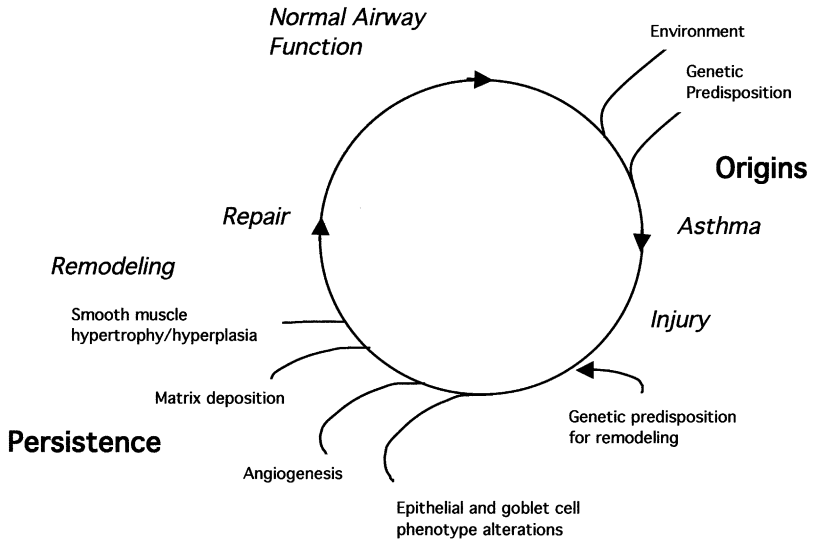

FIG 1. A model of aberrant injury-repair responses promoting irreversible airflow obstruction in asthmatic patients. Although both genetic predisposition and environmental factors are involved, it is plausible that a different genetic predisposition might promote an injury-repair response that increases the risk of airway remodeling and irreversible airflow obstruction. (Modified from a figure published in Lazaar AL, Panettieri RA. Is airway remodeling clinically relevant in asthma? *Am J Med.* 2003;115:652-9.)

glucocorticoids. Matthews et al[10] hypothesized that one mechanism for glucocorticoid resistance is failure of the glucocorticoid receptor to translocate into the nucleus and promote histone acetylation. They found a reduced ability of PBMCs to suppress TNF-α–induced GM-CSF, an activity mediated by histone acetyltransferase, in steroid-dependent and steroid-resistant patients compared with that seen in glucocorticoid-sensitive patients. PBMCs from steroid-dependent and steroid-resistant patients had decreased translocation of the glucocorticoid receptor to the nucleus and reduced histone acetylation. Other mechanisms have previously been reported,[11,12] and together this research supports the idea that genetics will lead to individualized approaches to patient care in the future.

Szczeklik et al[13] questioned whether polymorphisms of the promoter of the *COX2* gene affect binding of gene transcription factors and clinical relevance. Homozygotes for this allelic variant were more likely to be female and more likely to have increased production of 2 prostaglandins and more severe asthma in aspirin-intolerant asthma.

One of the most fascinating reports on pharmacogenetics comes from the National Heart, Lung, and Blood Institute Asthma Clinical Research Network.[14] In a prospective, randomized, double-blind, cross-over study of adults with mild asthma, they compared regularly scheduled albuterol in 2 sets of homozygotes for a functional polymorphism of the β_2-adrenergic receptor. Patients homozygous for an arginine at the 16th amino acid position of the receptor had lower morning peak expiratory flow rates during treatment with regularly scheduled albuterol, with a genotype-attributable treatment difference of 24 L/min (95% CI, −37 to −12). Thus avoiding albuterol might be appropriate for patients with the Arg/Arg genotype. These reports also point to the challenge of understanding the association between gene variability and phenotype in complex diseases like asthma.

Study design in genetics research. The study of genetic susceptibility and gene-environment interactions on the development of asthma is a major area of research. Two general approaches are used: genome-wide screens and candidate gene studies.[15,16] Genome-wide screens can be used to discover genetic markers in families associated with a clinical phenotype like asthma. The screen identifies a region, and finer mapping (positional cloning) is used to recognize variations in individual genes associated with a disease phenotype. Another approach starts by considering candidate genes, genes whose functions are known and related to asthma pathophysiology, and seeks polymorphisms within these genes. Case-control designs compare individuals with the disease phenotype with individuals without this phenotype.

Genetic susceptibility. Asthma susceptibility gene research provides clues to the underlying pathobiology of asthma.[17-20] Raby et al[17] conducted a family-based association study of *ADAM33* polymorphisms. *ADAM33* might play a role in airway remodeling in asthma that is resistant to corticosteroids.[21,22] Raby et al[17] found no single nucleotide polymorphism association with asthma. They indicated that previous conflicting reports could have used a population that was either too selective, the association could have occurred by chance, or the true asthma susceptibility locus could be near but not at the *ADAM33* location.

Hoffjan et al[23] studied wheezing infants with respiratory tract infections and the development of asthma and allergy. Genetic variations in cytokine response profiles (IL-5, IL-10, IL-13, and IFN-γ) and atopic phenotypes

were determined prospectively. A polymorphism of the β chain of the high-affinity IgE receptor *(FCER1B 237Gly)* and a polymorphism of nitric oxide synthase *(NOS2A)* were each associated with reduced IL-13 responses in cord blood; individuals having both polymorphisms had the lowest levels of IL-13 in cord blood. The *IL13 (IL13 110Gln)* allele was associated with increased IgE levels at year 1. An allelic variant of colony-stimulating factor was associated with a greater increase in IL-5 response in the first year.

Environmental influences

Gene-environment interactions influence the pathogenesis of complex diseases like asthma. Gene expression might be different in microenvironments (cellular) and macroenvironments and might change as environments evolve.[9]

Exposures to bacteria and other microorganisms. Eder et al[24] examined the genetic basis for the decreased prevalence of asthma in children raised on animal farms by examining single nucleotide polymorphisms of 2 toll-like receptor genes. Toll-like receptors are mediators of the innate immune system located on antigen-presenting cells and epithelial cells that bind to endotoxin and components of microorganisms prevalent on animal farms. The researchers hypothesized that children on farms have polymorphisms of receptors for these molecules that protect against asthma. They found that farmers' children carrying a polymorphism of *TLR2* were less likely to have asthma. No association was found among children from the same rural communities who did not live on farms. Questions to be addressed in further studies include whether nonfarmer parents were less likely to be atopic and whether other characteristics might affect asthma development, such as stress.[25]

Fageras Bottcher et al[26] examined polymorphisms of receptors for bacterial components, *TLR4* and *CD14*, for the association between polymorphisms of *TLR4* and *CD14* and asthma and allergic rhinitis. They reported lower LPS-induced IL-12 and IL-10 responses associated with a *TLR4* polymorphism and independently with asthma. However, there was no association with skin test reactivity or with other atopic diseases. These results conflict with those of Raby et al.[27] Bottcher et al[26] also assessed an association of *CD14/−159*, a polymorphism of the promoter region of the *CD14* gene, with the development of atopic symptoms. This polymorphism is associated with low levels of total serum IgE in children[28,29] and low levels of total serum IgE, decreased self-reported hay fever, and allergic rhinitis in adults. Bottcher et al could not find such an association. However, gene-environment interactions are ''extremely plastic,'' varying over time, environmental exposure, and location at which the gene is expressed, and could explain conflicting reports.[9]

Psychosocial exposures. Genetic susceptibility studies must consider other environmental influences on the development of asthma (eg, socioeconomic and psychologic stress). Wright et al[25] explored the association of caregiver stress with markers of the immune response in the first 2 to 3 months of a child's life. The PBMCs of these children, predisposed to atopy or asthma, had increased total IgE levels and an enhanced allergen-specific proliferative response when stimulated with mite and cockroach antigen. Higher levels of caretaker stress were associated with increased TNF-α levels and reduced IFN-γ levels in stimulated PBMCs. Stress and poor socioeconomic conditions could lead to poorer health.

Viral infection. Viral infection is thought to contribute to the development of asthma.[7,30-35] Heymann et al[30] compared, in a case-control study, 113 children aged 2 months to 18 years admitted for wheezing with 113 nonwheezing control subjects. Wheezing children less than 3 years of age tended to be admitted between December and March. Respiratory syncytial virus (RSV) was the predominant pathogen. Children older than 3 years tended to be hospitalized between September and November and to have evidence of atopy compared with control subjects.

Camara et al[31] studied 132 wheezing children from Brazil from birth to 12 years of age in a case-control study. In children younger than 2 years of age, RSV and family history of allergy were independently associated with wheezing. Interestingly, the RSV infections tended to occur in late summer and early to mid-autumn. Among children 2 to 12 years of age, they found allergy, as measured on the basis of positive serum levels of specific IgE, was the most important risk factor for wheezing. Rhinovirus infection was not associated with wheezing.

De Marco et al[32] conducted a retrospective study of 18,156 European asthmatic subjects aged 0 to 44 years. They found a family history of asthma or allergy and the occurrence of respiratory tract infections independently associated with a higher risk of asthma development. An atopic family history predicted a lower chance of remission throughout life. Wheezing associated with viral infection might be due to a combination of host (eg, atopy) and environmental (eg, rhinovirus) interactions with abnormal immune responses.[35]

Origins of asthma: Atopic disorders. The concept of atopic march suggests a progressive development of atopic diseases from infancy, beginning with atopic dermatitis and food allergy and progressing to allergic rhinitis and asthma.[36] Both Camara et al[31] and Heymann et al[30] found allergy to be a significant risk factor in children older than 2 or 3 years. In a prospective population-based cohort study from Germany, Illi et al[37] found that atopic dermatitis in infancy is associated with asthma at school age.[38] They reported that the onset of wheezing tended to occur before or at the onset of atopic dermatitis.[37] Guilbert et al[39] examined the atopic profile of 285 children between 2 and 3 years of age with frequent wheeze and a parental history of asthma or a personal history of atopic dermatitis. They found that 61% were sensitized to food allergens or aeroallergens, suggesting sensitization at a young age.[37,39] These studies do not examine the relationship of exposure to sensitization or sensitization to symptoms after allergen exposure. Although these and other studies collectively do not support an atopic march,[40-42] they do suggest that the

maturity of the immune system at the time of gene-environment interaction influences the development of asthma.

Developmental influences on prevention and course. With respect to primary prevention, Johnson et al,[43] in a birth cohort, found increased dust mite exposure during infancy was associated with a higher risk for sensitization if parents were atopic but had no protective effect among children whose parents were not atopic. Becker et al[44] conducted a randomized trial in 545 high-risk infants to reduce house dust mite, pet, and environmental tobacco smoke exposure. Breast-feeding was encouraged. Those in the intervention group were less likely than control infants to have asthma by the age of 2 years. Kull et al[45] found an association between breast-feeding and a reduction in the risk of asthma. Peat et al[46] considered whether the separate effects of dietary supplementation with omega-3-fatty acids and house dust mite avoidance were associated with primary prevention of asthma and reported a significant reduction in the prevalence of cough in atopic children with the active diet but no effect on cough among nonatopic children. Although there was a 7.2% reduction in sensitization to house dust mite in the intervention group, there was no difference in wheeze among study groups. More studies of primary prevention are necessary to better define the most effective preventive measures.

Concerning secondary prevention, Schatz et al,[47] in an analysis of maternal medications and adverse maternal and fetal events during pregnancy and postpartum from 2123 gestations, found no increase in perinatal risk with the use of inhaled β-agonists, inhaled steroids, or theophylline. Oral corticosteroid use was associated with birth at less than 37 weeks' gestation and low birth weight.

Novembre et al[48] conducted a randomized unblinded trial in 113 nonasthmatic children aged 5 to 14 years with allergic rhinitis limited to grass pollen to sublingual immunotherapy compared with standard symptomatic therapy. Children in the intervention group used less medication in years 2 and 3 and reported less severe symptoms. After 3 years, the control group was 3.8 times more likely to have asthma.

PERSISTENCE OF ASTHMA

Exacerbations

As previously noted, Heymann et al[30] concluded that viral infections were the dominant risk factor for wheezing among children hospitalized before 3 years of age, with RSV being the dominant pathogen during the winter months and rhinovirus during the other months. A large majority of the wheezing children aged 3 to 18 years had atopic characteristics that might be a major risk factor for hospitalization and an adverse response to viral infections, especially rhinovirus.

Rabinovitch et al[49] studied the association between levels of ambient air pollutants and asthma exacerbations in poor urban children with moderate-to-severe asthma. Ambient levels of Environmental Protection Agency criteria air pollutants in Denver did not lead to clinically significant asthma worsening in urban children during the winter months. Szema et al[50] examined the effect of the collapse of the World Trade Center on September 11, 2001, on local pediatric patients with asthma. Asthma severity worsened in pediatric patients living near Ground Zero, especially those within 5 miles of Ground Zero.

Factors contributing to the persistence of asthma

Sears et al[51] studied the outcome of childhood asthma in adults. Factors predicting persistence or relapse of asthma were sensitization to house dust mites, airway hyperresponsiveness, female sex, smoking, and early age of onset. De Blic et al[42] reported on the bronchial inflammatory profile in children with difficult asthma. In symptomatic children T_H2-type inflammation was associated with the presence of activated eosinophils in the epithelium, whereas asthma in children with few symptoms was associated with an increase in T_H1 cytokine levels, suggesting that perhaps high levels of IFN-γ, a T_H1 cytokine, might be modulating the local inflammatory response. Miranda et al[41] examined phenotypic differences between early-onset severe asthma and late-onset disease. Subjects with early-onset severe asthma had significantly more allergen sensitivity–induced eczema and more allergic symptoms than subjects with late-onset asthma. Presence of eosinophils was associated with low pulmonary function.

Chrischilles et al[52] sought to estimate asthma prevalence and morbidity in Iowa. They reported that asthma prevalence in children in a large rural population was comparable with that in large Midwestern cities, suggesting that rural life in itself does not reduce asthma risk. Van Stien et al[53] determined the level of indoor exposure to muramic acid–peptidoglycan and its potential association with respiratory health in a farm and nonfarm study population from Austria, Switzerland, and Germany. Muramic acid, a constituent of peptidoglycan, is present in gram-negative and gram-positive bacteria in the environment. Unlike endotoxin, muramic acid was inversely associated with wheezing, with no association with the prevalence of atopic sensitization. Their data support the proposed hygiene hypothesis because higher environmental exposure to bacteria was associated with a reduced prevalence of asthmatic symptoms.

Al-Mousawi et al[54] investigated risk factors in Kuwaiti children to understand the causes of asthma and sensitization in populations located in desert countries. Sensitization to allergens, family history of asthma, history of whooping cough, and current cat ownership increased the risk for asthma, whereas breast-feeding was protective. Members of the Inner-City Asthma Study[55] reported that the concentration of fungi was higher in homes with dampness problems, cockroach infestation, and cats. They reported that the indoor-outdoor difference in fungal concentrations could provide a valuable metric for epidemiologic investigations of the role of fungal exposure as a risk factor for disease. Matsui et al[56]

reported that mouse allergen exposure was common and sensitivity unexpectedly high among suburban middle-class children with asthma. Increasing bedroom levels of Mus m 1 and dog skin test sensitivity were risk factors for mouse skin test sensitivity.

Monitoring techniques for asthma control and persistent inflammation

Currently, the success of asthma management is determined on the basis of the reduction in symptoms and the frequency of exacerbations. However, there is growing unrest that these 2 measures might underestimate the degree of control. Nathan et al[57] introduced the Asthma Control Test, a 5-question test to provide a simple method for assessing asthma control with or without lung function testing. Bogen and Apter[58] indicated that a new electronic device could be applied to dry powder inhaler devices for assessing medication adherence.

Covar et al[59] evaluated the safety of induced sputum analysis for assessing inflammation. Sputum induction is a relatively noninvasive and safe procedure that can provide information on eosinophilic inflammation and treatment response and is also associated with several measures of asthma control and other markers of inflammation, including exhaled nitric oxide. Saito et al[60] conducted an epidemiologic study in children and concluded that exhaled nitric oxide can be used as a noninvasive marker of allergic airway inflammation in children. It was the best predictor for recurrent wheezers compared with other variables. Mahut et al[61] reported that the combination of pulmonary function and exhaled nitric oxide measures are useful as noninvasive assessments of uncontrolled eosinophilic inflammation and airway remodeling in children with refractory asthma.

Zanconato et al[62] measured leukotriene and 8-isoprostane values in exhaled breath condensates from children with asthma. Cysteinyl leukotriene and 8-isoprostene concentrations were higher in asthmatic children with unstable asthma than in healthy control children and could be useful in assessing phenotypic differences and the effect of intervention among asthma populations. They also reported that exhaled air temperature, possibly because of the release of proinflammatory cytokines, could reflect the level of airway inflammation in asthmatic children, but this hypothesis requires further evaluation.[63] Mondino et al[64] reported on the effects of inhaled corticosteroids (ICSs) on exhaled leukotriene and prostanoid concentrations in asthmatic children. Exhaled leukotriene (LT) E_4, LTB_4, and isoprostane values were increased in atopic asthmatic children but not in atopic nonasthmatic children.

Joseph-Bowen et al[65] examined the relationship of atopy, asthma, and eosinophilic inflammation using serum eosinophilic cationic protein (ECP). The higher ECP levels seen in 6-year-old children with current asthma and more severe atopy suggested that atopy and eosinophilic inflammation are important in driving this clinical phenotype. ECP levels were highest in children with severe asthma, especially in those with concurrent therapy.

MANAGEMENT OF ASTHMA IN CHILDREN, ADOLESCENTS, AND ADULTS

Effectiveness of environmental control and current therapies

Cabana et al[66] assessed the type and frequency of attempts by families to control environmental precipitants of symptoms and their degree of consistency with current guidelines. Improved awareness about recognized methods to address triggers might help families use more effective environmental control measures. Morgan et al[67] reported that an individualized, home-based, comprehensive environmental intervention was effective in decreasing exposure to indoor allergens, including cockroach and dust mite allergens, resulting in reduced asthma-associated morbidity.

On the basis of a nested case-control study, Corren et al[68] reported that in patients with asthma, treatment of concomitant allergic rhinitis was associated with significant reductions in emergency department treatment and hospitalization for asthma. Harrison et al[69] found no evidence to support the effects of doubling the dose of ICS when asthma deteriorates, answering an important clinical question. Williams et al[70] sought to examine the proportion of poor asthma-related outcomes attributable to ICS nonadherence. Poor adherence to ICS therapy among adult asthmatic patients was correlated with a number of poor asthma-related outcomes, including hospitalization.

Glucocorticoids have potent immunosuppressive properties but might be modulated by the local immune milieu. Tsitoura et al[71] suggested that mitogen-activated protein kinase inhibitors might offer a therapeutic solution for glucocorticoid resistance. Hanania et al[72] reported that the immune response to the A antigens of the inactivated influenza vaccine in subjects with asthma was not adversely affected by ICS therapy; however, high-dose ICS therapy might diminish the response to the B antigen of the vaccine.

Several rare adverse effects related to ICS therapy were reported this year, including 2 cases of myopathy associated with high-dose fluticasone therapy[73] and possible neuropsychologic changes caused by ICSs.[74] Nowak-Wegrzyn et al[75] reported on allergic reactions after the ingestion of lactose-containing medications in a patient with milk allergy, possibly because of milk protein contamination.

Other potential asthma control therapies

Oba and Salzman[76] reported that omalizumab could be cost saving if given to nonsmoking patients who are hospitalized 5 or more times or 20 days or longer per year despite maximal asthma therapy. Hunt et al[77] reported that nebulized lidocaine is safe and effective in patients with mild-to-moderate asthma. Lee et al[78] evaluated the effects of matrix metalloproteinases inhibiting antibiotic, doxycycline, and matrix metalloproteinase inhibitors on hyperresponsiveness and inflammation of the airways in toluene diisocyanate–induced asthma. Doxycycline might reduce airway inflammation and hyperresponsiveness through

TABLE I. Key advances

- Pharmacogenetic research suggests an explanation for varying responses of patients to asthma medications, such as corticosteroids and β-agonists.
- Genetic susceptibility studies in the past year show the importance of exploring the relationship between genetic variation and phenotype.
- On the basis of a large study of asthma in pregnancy, there was no increase in perinatal risk with the maternal use of inhaled β-agonists, inhaled steroids, or theophylline; oral corticosteroid use was associated with both birth at less than 37 weeks' gestation and low birth weight.
- Doubling the dose of inhaled steroids when asthma deteriorates does not improve clinical course.
- Viral infections tend to be the dominant risk factor for wheezing illness among children hospitalized before 3 years of age with RSV, the dominant pathogen, during the winter months and rhinovirus during the other months. In later years, there is an increased association of atopy with subsequent development of asthma.
- Viral infection, in addition to contributing to asthma exacerbations, might have a role in the development of asthma.

the phosphatidylinositol 3–kinase pathway on the basis of this murine model of toluene diisocyanate–induced asthma. Kawano et al[79] evaluated the effects of tacrolimus in aspirin-induced asthma. Tacrolimus inhibited bronchoconstriction and abrogated the aspirin-induced increase in both sputum ECP and urinary LTE_4 levels. These observations prompt further studies for clinical application.

New directions in treatment: Establishing control

Bateman et al[80] compared the effect of fluticasone propionate and salmeterol-fluticasone in achieving asthma control over a 1-year study period. Significantly more patients in each stratum (previously corticosteroid-free low- and moderate-dose corticosteroid users) achieved control with salmeterol-fluticasone than with fluticasone alone. The approach of aiming for total control and maintaining treatment resulted in the virtual elimination of exacerbations and near-normal quality of life in the majority of patients and brought substantial benefit even to those who failed to achieve this high level of control.

CONCLUSIONS

Over the last 20 years, the treatment of asthma has changed from a trial-and-error approach to one that is evidence based. With the recognition that asthma is a heterogeneous disease, current research is being directed to understanding the natural history of the disease and to identifying methods to differentiate pathways of disease activity. It is possible that the application of genetics and biomarkers of airway inflammation might be useful in guiding management strategies. Continued attention must now be directed to understanding the origins and persistence of asthma, along with effective interventions and methods to monitor disease activity, as summarized in these recent journal reports (Table I). Furthermore, understanding patients who fail current therapeutic approaches could lead to new drug discovery.

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Correction

With regard to the January 2005 *Quick Reference* article entitled ''Managing asthma during pregnancy: Recommendations for pharmacologic treatment—2004 update'' (2005;115:34-46): The full version of this NAEPP Expert Panel Report, including all of the evidence tables, is available at http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm.