

Year in Review

Asthma, Airway Biology, and Nasal Disorders in AJRCCM 2002

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ALLERGIC RHINITIS AND NASAL DISORDERS

Nasal Function

The paranasal sinuses are major producers of nitric oxide. To determine whether oscillating airflow induced by humming would increase nasal levels of nitric oxide, Weitzberg and Lundberg (1) studied ten healthy subjects. Compared with quiet exhalation, humming caused a 15-fold increase in the level of nasal nitric oxide: 252 versus 17 parts per billion. In a two-compartment model of the nose and sinus, oscillating airflow caused a dramatic increase in gas exchange between the cavities. Because obstruction of the sinus ostium is a central event in sinusitis, measurement of nasal nitric oxide during humming may provide a useful test of ostial patency. The authors conclude that humming provides a dramatic increase in sinus ventilation and nasal release of nitric oxide. An editorial commentary by Cardell (2) accompanies this article.

ASTHMA AND AIRWAY BIOLOGY

Genetics

To determine whether the occurrence and severity of asthma in first-degree relatives of patients with asthma is related to the severity of asthma in the index case, Pin and coworkers (3) analyzed data from 944 subjects (348 cases, 329 relatives with asthma, and 357 subjects without asthma) and 3,467 first-degree relatives of probands. Compared with relatives of subjects without asthma, the risk of asthma among relatives of pediatric and adult cases of asthma was increased (odds ratio of 3.4 and 4.5, respectively). The risk of asthma among relatives was not related to the severity of asthma in the cases. When asthma occurred among relatives, there was significant familial resemblance for a clinical severity score (intraclass correlation coefficients of 0.23 for both pediatric and adult cases) and for forced expiratory volume in one second (FEV₁; intraclass correlation coefficients of 0.19 and 0.25 for pediatric and adult cases, respectively). The authors conclude that first-degree relatives of patients with asthma have an increased risk of asthma, but that the risk of occurrence is not related to the severity of asthma in the index cases, although the severity of asthma displays a familial resemblance.

The *TNFA* gene, which encodes tumor necrosis factor- α , and the *TNFB* gene, which encodes tumor necrosis factor- β , are located within the region encoding the major histocompatibility complex on chromosome 6p21.3. To determine whether a polymorphism in the 5' flanking region of the *TNFA* gene and an *NcoI* polymorphism on the *TNFB* gene are associated with the development of asthma, Noguchi and coworkers (4) did transmission disequilibrium tests on 144 families identified through children with atopic asthma. Transmission of the -857C allele and the -1031T-863C-857C haplotype in the *TNFA* gene to offspring affected by asthma occurred more frequently than ex-

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pected. The *LTA NcoI* polymorphism was not associated with the development of asthma. The authors conclude that the -857C allele and the -1031T-863C-857C haplotype of the gene for tumor necrosis factor- α is associated with the development of atopic asthma in childhood.

Glutathione *S*-transferase M1 participates in pathways involved in the pathogenesis of asthma, such as xenobiotic metabolism and antioxidant defenses. To determine whether the genotype for glutathione *S*-transferase M1 and *in utero* exposure to maternal smoke influence the occurrence of asthma, Gilliland and coworkers (5) studied 2,950 fourth, seventh, and tenth grade children. The effects of *in utero* exposure to maternal smoking on asthma and wheezing were largely restricted to children with the null genotype for glutathione *S*-transferase M1. Among children with the null genotype, *in utero* exposure to maternal smoking was associated with an increased prevalence of early onset asthma (odds ratio, 1.6), asthma with current symptoms (odds ratio, 1.7), persistent asthma (odds ratio, 1.6), lifetime history of wheezing (odds ratio, 1.8), wheezing with exercise (odds ratio, 2.1), wheezing requiring medication (odds ratio, 2.2), and emergency room visits in the preceding year (odds ratio, 3.7). *In utero* exposure to smoking was not associated with asthma or wheezing in children who were positive for the glutathione *S*-transferase M1 genotype. The authors conclude that the adverse effects of *in utero* exposure on asthma and wheezing are largely restricted to children with the null genotype for glutathione *S*-transferase M1.

RANTES (regulated upon activation, normal T cell expressed and secreted) is a CC chemokine that attracts eosinophils, basophils, mast cells, and T cells during immune responses. Because the -403A and -28G alleles of the RANTES promoter region exhibit enhanced promoter activity in reporter constructs *in vitro*, Hizawa and coworkers (6) investigated the influence of these alleles on the development of asthma using a case-control analysis (298 patients with asthma and 311 control subjects). The -28G allele was associated with late-onset asthma (after 40 years of age; odds ratio, 2.03), but not with asthma of earlier onset. The -403A allele was not associated with asthma. Subjects who carried the -28G allele also displayed increased production of RANTES *in vitro*. The authors conclude that the -28G allele of the RANTES promoter region is associated with increased susceptibility to late-onset asthma.

Epithelium-specific ETS-2 and ETS-3 are transcription factors that have been proposed as candidate genes for asthma. To determine whether sequence variants of these genes are associated with asthma, Baron and coworkers (7) conducted a case-control association analysis. The sample consisted of 311 white subjects with asthma and 177 white subjects without asthma. Seven noncoding or synonymous single-nucleotide polymorphisms were detected: three in epithelium-specific ETS-2, and four in epithelium-specific ETS-3. Logistic regression, adjusted for age and sex, suggested a weak association between one epithelium-specific ETS-2 polymorphism and a diagnosis of asthma (odds ratio, 1.89). Total serum immunoglobulin E and predicted FEV₁ were not associated with any of the polymorphisms. Extended haplotyping indicated linkage disequilibrium in these genes, although no association or epistatic interaction was found. The authors conclude that epithelium-specific ETS-2 and ETS-3 are unlikely to contain polymorphic loci that have a major impact on susceptibility to asthma.

The toll-like receptor 4 is the principal receptor for recognition of bacterial endotoxin in humans and mice, and functional variants in the gene for the receptor confer a decrease in responsiveness to endotoxin. Because exposure to endotoxin in early life appears to protect against the development of atopy and asthma, Raby and coworkers (8) determined whether genetic variation in the locus for toll-like receptor 4 contributes to

asthma susceptibility. In a cohort of 90 ethnically diverse subjects, the toll-like receptor 4 locus was resequenced, and a total of 29 single nucleotide polymorphisms were identified. Five common polymorphisms were assessed for evidence of an association with asthma in two large family-based cohorts: a heterogeneous North American cohort (589 families) and a more homogenous population from northeastern Quebec, Canada (167 families). The transmission-disequilibrium test revealed no evidence of an association for any of the polymorphisms tested. The toll-like receptor 4 variants were not associated with four qualitative, intermediate asthma-related and atopy-related phenotypes. The authors conclude that there is no evidence that genetic variation in toll-like receptor 4 contributes to asthma susceptibility.

In a pulmonary perspective, Palmer and colleagues (9) discuss the pharmacogenetics of asthma.

Epidemiology

To describe the natural history of atopic and wheezy disorders, Rhodes and coworkers (10) enrolled 100 subjects at birth on the basis that at least one parent had atopy. Sixty-three percent of the subjects were studied at 22 years of age. The annual prevalence of both wheeze and bronchial hyperresponsiveness to histamine increased with age, and 25% of adults had asthma. Remission of wheeze was common in children younger than 5 years, but wheeze was likely to persist if it was present at 11 years. Of adults with asthma, 60% developed sensitivity to common allergens by 2 years of age and displayed bronchial hyperreactivity by 11 years of age. The authors conclude that adults with asthma can begin to wheeze at any age, but they tend to sensitize early and display bronchial hyperreactivity by 11 years of age.

To determine the role of indoor allergen sensitization and exposure as a cause of morbidity in women with asthma, Lewis and coworkers (11) studied 458 women from Boston (140 of whom had asthma) over a 4-year period. Women with asthma who had elevated levels of specific IgE to cat or cockroach allergens reported greater morbidity in the preceding year if high levels of a relevant allergen were found in dust samples from the home. Women with asthma sensitized to cat allergen and with concentrations of greater than 8 μ g per gram in the home samples were more likely to have used glucocorticoids (odds ratio, 2.7) and to have wheezed without a cold (odds ratio, 6.8). Women sensitized to cockroach and exposed to cockroaches were at least three times more likely to have used glucocorticoids and to have visited an emergency room. The authors conclude that cockroach and cat allergens contribute to asthma morbidity in sensitized women.

To determine the interrelationship between current and past infection with *Ascaris lumbricoides* and asthma and atopy, Palmer and coworkers (12) studied a cross-sectional sample of 2,164 children between the ages of 8 and 18 years from rural China. The prevalence of either a history or positive stool examination for *Ascaris* was 24.5%. Independently of other factors, infection with *Ascaris* was associated with increased risk of asthma (odds ratio, 1.85), increased number of skin tests positive to aeroallergens (odds ratio, 1.25), and an increased slope of the dose-response to methacholine. The authors conclude that infection with *Ascaris lumbricoides* is associated with an increased risk of childhood asthma, increased airway hyperresponsiveness, and sensitization to common aeroallergens.

To determine the relationship between exposure to microbial load during pregnancy and the development of allergic disease, McKeever and coworkers (13) analyzed data from a birth cohort of 24,690 children. Exposure to antibiotics *in utero* was associated with an increased risk of asthma in a dose-related manner. Compared with no antibiotics, more than two courses of antibiotics was associated with increased risk of asthma (hazard ratio, 1.68),

eczema (hazard ratio, 1.17), and hay fever (hazard ratio, 1.56). Exposure to a range of infections *in utero* was associated with a small increased risk of developing allergic disease. The presence of an older sibling had a strong protective effect on the incidence of allergy. The authors conclude that exposure to antibiotics *in utero* is associated with a dose-related increase in the risk of allergic disease in children.

To characterize the burden of asthma in the United States, Fuhlbrigge and coworkers (14) did a telephone survey of 42,022 households to identify adults with asthma or parents of children with asthma. The burden consisted of three components: short-term burden (4-week recall); long-term burden (1-year recall); and functional impact (limitation of activity). Only 10.7% of individuals with asthma were classified as having mild intermittent asthma; 77.3% were classified as having moderate to severe persistent asthma. The discordance in type and distribution of symptoms of asthma among individuals demonstrates that an exact estimate of asthma burden depends on how a classification is operated. The authors conclude that the burden of asthma on health and functioning of the U.S. population is substantial, and that most patients have persistent asthma rather than mild intermittent asthma.

Airway Inflammation

Animal models. Children raised in the homes of cigarette smokers have a higher incidence of asthma than do children raised by nonsmokers. To understand the mechanisms involved, Barrett and coworkers (15) developed an experimental model. Pregnant mice were exposed to either air or mainstream cigarette smoke (6 hours every day) during pregnancy. The newborn mice were exposed for 4 weeks to either air or sidestream cigarette smoke (6 hours a day for 5 days a week), and then exposed over the subsequent 6 weeks to air, sidestream smoke, aerosolized ovalbumin, or a combination of smoke plus ovalbumin. Aerosolized ovalbumin caused increased airway hyperresponsiveness, increased total IgE, increased ovalbumin-specific IgE and IgG₁, and increased lymphocytic and neutrophilic inflammation in the lungs of offspring that were genetically predisposed to respond to ovalbumin without prior exposure (hemizygotes, +/-, for the ovalbumin-T cell receptor). Aerosolized ovalbumin did not cause airway hyperresponsiveness in offspring that were not genetically predisposed to respond to ovalbumin (transgene -/- mice) unless it was delivered in conjunction with sidestream smoke. Sidestream smoke alone caused airway hyperresponsiveness in both transgene +/- and -/- offspring. Among the transgene +/- offspring, those exposed to both ovalbumin and sidestream smoke had decreased total IgE, and ovalbumin-specific IgE and IgG₁ as compared with those exposed to ovalbumin alone. The authors conclude that exposing newborn mice to sidestream smoke produces airway hyperresponsiveness in offspring that were both predisposed and not predisposed to develop an allergic response to ovalbumin, and that the hyperresponsiveness was not associated with increased pulmonary eosinophilia.

The appropriateness of mice as a model of human airway disease is debated by Gelfand (16) and Persson (17), with rebuttals from each (18, 19).

Induced sputum. Lipoxins are endogenous eicosanoids produced by lipoxygenase that have an antiinflammatory action. To determine the role of lipoxins, Bonnans and coworkers (20) obtained induced sputum samples from 10 patients with severe asthma, 10 patients with mild asthma, and 8 healthy subjects. Interleukin-8 was higher in the patients with severe asthma, 5.1 ng per ml, than in patients with mild asthma, 1.4 ng per ml, or healthy subjects, 0.2 ng per ml. Lipoxin A₄ was higher in patients with mild asthma, 1.3 ng per ml, than in patients with severe asthma, 0.8 ng per ml, or control subjects, 0.1 ng per ml. The

level of lipoxin A₄ was correlated with the level of interleukin-8 only in the patients with mild asthma ($r = 0.82$). In *in vitro* experiments, the release of interleukin-8 from peripheral blood mononuclear cells from both groups of patients was inhibited by nanomolar concentrations of lipoxin A₄ and lipoxin B₄. Messenger RNA for lipoxin A₄ receptor was expressed on peripheral blood monocytes from both groups of patients. The authors conclude that persistent airway inflammation in patients with severe asthma is associated with a deficiency of antiinflammatory mediators such as lipoxins.

Bronchial and bronchoalveolar specimens. In the renal tubular epithelium, glutaminase neutralizes acid by converting glutamine to ammonia. In epithelial cells from the human airway, Hunt and coworkers (21) demonstrated *in vitro* biochemical activity of glutaminase and the expression of messenger RNA for two isoforms of the enzyme. *In vivo* studies revealed expression of glutaminase protein in the human airway. Glutaminase activity was increased by acidic stress, which resulted in increased cell survival, and inhibited by interferon- γ and tumor necrosis factor- α . In 30 patients with acute asthma, ammonia levels in breath condensates were 10% of the levels in 24 healthy subjects and were correlated with the pH of the condensate ($r = 0.58$). The authors conclude that glutaminase is expressed and is active in human airway epithelium, and that the production of ammonia protects against acidic stress and is inhibited by inflammatory cytokines. An editorial commentary by Griffith (22) accompanies this article.

The calcium-activated chloride channel 1 plays a role in intestinal transport of fluid and electrolytes, and its mouse counterpart, gob-5, is involved in mucus hyperproduction in murine models of asthma. To investigate its involvement in human asthma, Hoshino and coworkers (23) did bronchial biopsies in 21 patients with asthma and 13 healthy subjects. The channel was significantly upregulated in patients as compared with the healthy subjects, and it was located especially in the mucus-producing goblet cells of the epithelium. The *in vitro* transfection of a vector expressing calcium-activated chloride channel 1 into a human mucoepithelial cell line, NCI-H292, caused increased mucus production and induced the MUC5AC gene. The authors conclude that calcium-activated chloride channel 1 plays a direct role in mucus production and the differentiation of goblet cells in patients with asthma.

Histone deacetylases consist of at least ten enzymes associated with suppression of gene expression, whereas acetylation of histones by histone acetyltransferases is associated with increased gene transcription. To study the distribution, expression, and activity of histone deacetylases, Ito and coworkers (24) did bronchial biopsies in 26 patients with asthma and 14 healthy subjects. The site of expression of histone deacetylases 1 to 6 did not differ between the patients and the healthy subjects, although the patients had decreased enzymatic activity and decreased protein expression of histone deacetylase 1 and 2. Patients treated with inhaled glucocorticoids had greater activity of histone deacetylase than did untreated patients, but still less than did the healthy subjects. The site of expression of histone acetyltransferase was unaltered in the patients with asthma, although activity was increased. Patients treated with inhaled glucocorticoids had normal levels of histone acetyltransferase. The authors conclude that patients with asthma have decreased activity of histone deacetylases and increased activity of histone acetyltransferase, and that these changes may contribute to regulation of inflammatory gene expression in the airways of patients with asthma. An editorial commentary by Sterk and Koenderman (25) accompanies this article.

Blood. Dendritic cells, the most potent antigen-presenting cells, play a central role in initiating the primary immune re-

sponse. Myeloid (Type 1) dendritic cells preferentially cause naive T cells to differentiate into Type 1 (Th1) helper T cells, and plasmacytoid (Type 2) dendritic cells preferentially cause naive T cells to differentiate into Type 2 (Th2) helper T cells. To determine whether subsets of dendritic cells are altered in patients with asthma, Matsuda and coworkers (26) obtained peripheral blood from 44 patients with asthma and 38 normal subjects. The number of plasmacytoid (Type 2) dendritic cells was higher in the patients with asthma than in the normal subjects (5.8 versus 3.0 per μl). The ratio of myeloid to plasmacytoid dendritic cells was lower in patients with asthma than in the normal subjects (3.7 versus 6.7). The authors conclude that patients with asthma have a higher proportion of plasmacytoid (Type 2) dendritic cells, which may contribute to the Th2-dominant immune phenotype in asthma.

Chemokines that act on CC-chemokine receptor 3 play important roles in the regulation of eosinophils, basophils, and, potentially, the recruitment of Type 2 (Th 2) helper T cells and mast cells. Bryan and coworkers (27) studied the action of eotaxin and other chemokines on multiple leukocyte populations in whole blood. The potency of eotaxin in whole blood was limited by Duffy antigen binding. A new panel of small molecule antagonists of CC-chemokine receptor 3 caused selective and potent inhibition of CC-chemokine receptor 3 on eosinophils and basophils, and was bioavailable in blood. The authors conclude that small molecule antagonists of CC-chemokine receptor 3 are potential candidates for prevention of eosinophil, basophil, Type 2 (Th2) helper T cell, and mast cell influx into airways.

Exhaled nitric oxide. Delclaux and coworkers (28) examined whether measurement of exhaled nitric oxide at multiple expiratory flow rates could differentiate bronchial and alveolar sources of the gas. Maximal bronchial output of nitric oxide was higher in 28 patients with asthma than in 36 healthy subjects: 133 versus 37 nl per minute. Alveolar concentration of nitric oxide was higher in 26 patients with cirrhosis than in the healthy subjects: 8.3 versus 4.7 ppb. The alveolar concentration was correlated with the alveolar-to-arterial gradient of Po_2 in the patients with cirrhosis. The authors conclude that a two-compartment model for the output of nitric oxide can differentiate between a bronchial and alveolar source of exhaled nitric oxide.

To assess the importance of expiratory flow rate on the diagnostic accuracy of exhaled nitric oxide, Deykin and coworkers (29) assessed several online and offline collection techniques in 34 patients with asthma and 28 healthy subjects. Expiratory flow rates of 50 to 500 ml per second were used in the offline collection techniques in the overall group; flows of 47 to 250 ml per second were also evaluated using online techniques in 18 patients with asthma and 17 healthy subjects. The fraction of exhaled nitric oxide fell with increasing expiratory flow rate. At each flow rate, exhaled nitric oxide was higher in the patients than in the control with both the online and offline techniques. Receiver operating characteristic (ROC) curves indicated that exhaled nitric oxide provided good discrimination between patients and control subjects: areas under the curve were 0.84 with the slowest online flow rate and 0.80 with the fastest offline flow. The authors conclude that exhaled nitric oxide provides robust discrimination between patients with asthma and healthy subjects, and that the exhaled flow can be selected for comfort and convenience, but it must be retained for repeated measurements.

Other exhaled markers. Kostikas and coworkers (30) assessed the relationship between the pH of expired breath condensates and airway inflammation in patients with a variety of lung diseases. The pH in expired breath condensates was lower in 20 patients with bronchiectasis (7.11) and in 20 patients with COPD (7.16) than in 40 patients with asthma (7.43) or in 10 healthy subjects (7.57). The pH was lower in 20 patients with moderate

asthma (FEV_1 60% of predicted) than in 20 patients with milder asthma. Values of pH were correlated with neutrophilia in the patients with COPD ($r = -0.66$) and in the patients with bronchiectasis ($r = -0.84$). Values of pH were correlated with exhaled hydrogen peroxide, a measure of oxidative stress, in patients with COPD ($r = -0.74$) and in patients with bronchiectasis ($r = -0.87$). In patients with moderate asthma, pH in expired breath condensate was correlated with sputum neutrophilia, oxidative stress, and total nitrate/nitrite. The authors conclude that monitoring the pH of expired breath condensates offers a means of assessing airway inflammation. An editorial commentary by Gaston and Hunt (31) accompanies this article.

In 20 healthy subjects, Effros and coworkers (32) studied the electrolyte and buffer concentrations of solutes present in exhaled condensates. The total ionic concentration was 497 μM . Of this concentration, 46% was ammonium. Little ammonium was found in condensates from three patients with tracheostomies, indicating that it is generated in the mouth. The concentrations of sodium, potassium, and chloride were well correlated with one another over a 200-fold range of concentrations. The concentrations of solutes in respiratory fluid were less than 2% of the concentrations in plasma. The authors conclude that exhaled condensates contain significant amounts of ammonium, and most of it is generated in the mouth. An editorial commentary by Hyde (33) accompanies this article.

Because patients with asthma have increased vascularity of the airway mucosa, Paredi and coworkers (34) assessed whether the temperature of exhaled gas is increased in asthma. The plateau temperature at end-exhalation was equivalent in 18 patients with asthma and in 16 healthy subjects (36 versus 34°C). The rate of increase in temperature (calculated between the onset of exhalation and 63% of the total increase in temperature) was greater in the patients with asthma than in the control subjects (8.2 versus 4.2°C per second), and it was correlated with the concentration of exhaled nitric oxide ($r = 0.65$). Inhalation of albuterol produced a 76% increase in the rate of rise of exhaled temperature in the healthy subjects, but no change in the patients with asthma. The authors conclude that patients with asthma have a faster rate of increase in the temperature of exhaled air than do healthy subjects, and that the rate of increase is correlated with the concentration of exhaled nitric oxide.

Antczak and coworkers (35) determined whether patients with aspirin-induced asthma have abnormal levels of eicosanoids in exhaled air condensates. Cysteinyl-leukotrienes were higher in 17 steroid-naïve patients with aspirin-induced asthma (152 pg per ml) than in 26 steroid-naïve patients with aspirin-tolerant asthma (37 pg per ml) or in 16 healthy subjects (19 pg per ml). Steroid-naïve patients with aspirin-induced asthma had higher levels of 8-isoprostane, a measure of oxidative stress, than did the healthy subjects: 132 versus 22 pg per ml. Both cysteinyl-leukotrienes and 8-isoprostane were lower in patients with aspirin-induced asthma who were treated with glucocorticoids. The levels of prostaglandin E_2 or leukotriene B_4 did not differ between the patient groups. The authors conclude that cysteinyl-leukotrienes and 8-isoprostanes are elevated in expired breath condensates of steroid-naïve patients with aspirin-induced asthma, and that glucocorticoids decrease the levels of cysteinyl-leukotrienes.

Ex vivo studies. Nahm and coworkers (36) sought to determine the role of autoimmunity in patients with nonallergic asthma (defined as negative skin tests to 50 aeroallergens and normal serum total IgE). IgG autoantibodies to a 49-kD antigen in cultured human bronchial epithelial cells (BEAS-28) were found in the sera of 43% of 23 patients with nonallergic asthma, 11% of 27 patients with allergic asthma, 10% of 20 patients with systemic lupus erythematosus, and 9% of 34 healthy subjects.

On amino acid sequencing, the protein was identified as cytokeratin 18. The authors conclude that human cytokeratin 18 antigen is a bronchial epithelial autoantigen associated with nonallergic asthma.

Cysteinyl leukotrienes cause airway smooth muscle cells to contract and proliferate, but it is not known whether they cause them to migrate. Parameswaran and coworkers (37) studied this phenomenon in cultures of airway smooth muscle cells obtained from the large airways of asthma-free patients undergoing lung resection. Platelet-derived growth factor-BB caused a 3.5-fold increase in the migration of the smooth muscle cells across a membrane. Leukotriene E_4 promoted the chemokinesis, but it did not promote chemotaxis. Priming with leukotriene E_4 produced a 1.5-fold increase in the migratory action of platelet-derived growth factor-BB. This action was blocked by the cysteinyl leukotriene receptor antagonist, montelukast. The priming effect was also partially attenuated by prostaglandin E_2 . Both the chemokinetic and the chemotactic "primed" responses were equally attenuated by an inhibitor of p38 mitogen-activated protein kinase and by an inhibitor of Rho-kinase. An inhibitor of phosphatidylinositol-3 kinase caused greater inhibition of the chemotactic response than of the chemokinetic response. The authors conclude that cysteinyl leukotrienes augment the migration of airway smooth muscle cells, and that the phosphatidylinositol-3 kinase pathway participates in the signaling of chemotactic migration of smooth muscle cells in response to cysteinyl leukotrienes.

Clara cell secretory protein (CCSP) is abundantly expressed within the epithelial cells of the conducting airways, and is believed to have immunoregulatory functions. Reynolds and coworkers (38) sought better understanding of the heterogeneity among secretory cells of the steady-state and injured mammalian lung. They used an expressed sequence tag, W82219 (also known as SCGB3A2), the expression of which is induced within Clara cells of CCSP knockout mice; the tag is distantly related to CCSP and it represents a member of a new subfamily of secretoglobins (MmSCGB3A2). Another member of the mouse SCGB3 family (Mm SCGB3A1) as well as human orthologs (HsSCGB3A and HsSCGB3A2) that possess structural homology to CCSP were identified, suggesting that they may share functional properties. Messenger RNA for SCGB3A1 was localized to a subset of SCGB3A2-expressing cells within bronchi of both mouse lungs and neonatal human lungs. CCSP, SCGB3A1, and SCGB3A2 were decreased in airways of neonates with bronchopulmonary dysplasia and in mice after airway injury. The authors conclude that two members of the secretoglobin gene family, SCGB3A1 and SCGB3A2, define molecularly distinct subsets of secretory cells within the epithelium of the conducting airways.

Review articles. A comprehensive series of review articles focusing on oxidants and antioxidants arose from a symposium on this subject (39–50).

Airway Hyperreactivity

Animal models: antigen challenge. To determine whether blockade of interleukin-9 might be useful in the treatment of asthma, Cheng and coworkers (51) studied its effects in a murine model. In mice sensitized to ovalbumin, aerosolized ovalbumin caused increases in airway hyperreactivity, numbers of inflammatory cells, and levels of interleukin-4, interleukin-5, and interleukin-13 in bronchoalveolar fluid. Intravenous administration of an antibody to interleukin-9 (given 30 minutes before the challenge) prevented the airway hyperreactivity, reduced the numbers of eosinophils and lymphocytes, and reduced the levels of interleukin-4, interleukin-5, and interleukin-13 in bronchoalveolar fluid. Blockade of interleukin-9 also decreased the expression of macrophage-derived cytokine in the airways. The authors conclude

that blockade of interleukin-9 in ovalbumin-sensitized mice decreases the secretion of interleukin-4 and interleukin-5, the accumulation of eosinophils and lymphocytes, and airway hyperreactivity that develop in response to an allergen challenge.

The synthesis of prostaglandin and thromboxane mediators depends on two isoforms of cyclooxygenase: constitutive cyclooxygenase-1 and inducible cyclooxygenase-2. Oguma and coworkers (52) studied the kinetics of these isoforms in the lungs of guinea pigs that were sensitized to ovalbumin and then challenged with ovalbumin. Within 1 hour after the challenge, the animals showed a robust and transient induction of messenger RNA expression for cyclooxygenase-2, but not for cyclooxygenase-1. This was followed by upregulation of the level and activity of cyclooxygenase-2 protein. Lung slices from the challenged animals released more prostaglandin D_2 and prostaglandin E_2 , either spontaneously or in response to A23187, than did slices from unchallenged animals. Selective inhibitors of cyclooxygenase-2 blocked the response and reduced the accumulation of eosinophils and neutrophils in the lungs. The authors conclude that allergen challenge causes expression of cyclooxygenase-2, and this isoform modulates prostanoid synthesis in the lung and airway pathophysiology.

Mice deficient in interleukin-10 develop significant pulmonary inflammation after allergen challenge, but do not develop airway hyperresponsiveness. Makela and coworkers (53) studied the effect of infection with respiratory syncytial virus in this setting. When interleukin-10-deficient mice were sensitized to ovalbumin, challenged with ovalbumin, and infected with respiratory syncytial virus, they developed airway hyperresponsiveness, increased eosinophils in bronchoalveolar fluid and pulmonary tissue, and mucin production in airway epithelium. Neither the combination of sensitization and challenge alone nor infection alone induced airway hyperreactivity. The interleukin-10-deficient mice displayed a type 1 (Th1) helper T cell response after sensitization and challenge with ovalbumin, but more of a type 2 (Th2) helper T cell response (increased levels of interleukin-5 in bronchoalveolar fluid) after infection with respiratory syncytial virus. The authors conclude that infection with respiratory syncytial virus overcomes the failure to develop airway hyperresponsiveness after allergen challenge in mice that are deficient in interleukin-10.

The cytokines interleukin-3, granulocyte macrophage colony-stimulating factor, and interleukin-5 contribute to inflammation in asthma, and their effects are mediated by receptors that share a common β_c subunit. Allakhverdi and coworkers (54) determined whether an antisense oligodeoxynucleotide could be used to block this receptor. (Antisense oligodeoxynucleotides are used to selectively inhibit the expression of a variety of genes.) An antisense phosphorothiolate oligodeoxynucleotide was found to specifically inhibit transcription of the common β_c subunit in bone marrow cells of rats, and it also inhibited expression of messenger RNA for the subunit within the lungs of rats when injected intravenously. Compared with control rats, inhibition of the common β_c subunit reduced the eosinophilia that occurs with antigen challenge in ovalbumin-sensitized rats, and it inhibited airway hyperresponsiveness to leukotriene D_4 . The authors conclude that the common β_c subunit of receptors for interleukin-3, interleukin-5, and granulocyte macrophage colony-stimulating factor modulates the eosinophil influx and airway hyperresponsiveness that follows a challenge with ovalbumin.

In mice sensitized with ovalbumin, nonselective inhibition of cyclooxygenase causes an increase in the type 2 (Th2) cytokines interleukin-5 and interleukin-13. Peebles and coworkers (55) investigated the role of the two cyclooxygenase isoforms on the allergic response. Sensitization of mice with ovalbumin caused expression of cyclooxygenase-2 protein, but not of cyclooxyge-

nase-1 protein. Selective inhibition of either cyclooxygenase 1 (SC58560) or cyclooxygenase 2 (SC58236) caused greater airway hyperresponsiveness in sensitized mice and higher levels of interleukin-13 in lung supernatant than in untreated sensitized mice. Sensitized animals treated with the cyclooxygenase 2 inhibitor or indomethacin (an inhibitor of both cyclooxygenase-1 and cyclooxygenase-2) had increased levels of messenger RNA for the chemokine receptors, CCR1 through CCR5 (expressed on eosinophils, basophils, lymphocytes, and dendritic cells), in the lung. The authors conclude that allergic inflammation in the lung increases the expression of inducible cyclooxygenase-2, but not of constitutive cyclooxygenase-1, and that inhibition of isoforms of the enzyme increases airway hyperresponsiveness and inflammation during allergen exposure. An editorial commentary by Peters-Golden (56) accompanies this article.

The late airway response in allergic rats is dependent on the leukotriene pathway. Nag and coworkers (57) investigated whether upregulation of cellular immunity with interleukin-2 affects airway reactivity to leukotrienes. Pretreatment of ovalbumin-sensitized rats with interleukin-2 for 4.5 days increased the airway responsiveness to inhaled leukotriene D₄. The enhanced late response to ovalbumin induced by interleukin-2 was blocked by montelukast, an antagonist of the cysteinyl leukotriene receptor. Montelukast decreased the expression of messenger RNA for interleukin-4 in the lungs and it increased expression of messenger RNA for interferon- γ . The authors conclude that upregulation of cellular immunity with interleukin-2 increases the sensitivity of the airways to leukotriene D₄, and that inhibition of the leukotriene pathway blocks the late response and modulates cytokine expression after antigen challenge.

Galectin-3 is an IgE-binding protein that binds to B-galactosides and induces selective downregulation of interleukin-5 gene expression in several cell types (eosinophils, T cell lines, and antigen-specific T cells). To determine the role of galectin-3 in airway inflammation and hyperreactivity, del Pozo and coworkers (58) exposed ovalbumin-sensitized rats to aerosolized ovalbumin. Compared with control rats, intratracheal instillation of plasmid DNA encoding galectin-3 lowered the eosinophil and T cell counts in bronchoalveolar fluid, inhibited messenger RNA for interleukin-5 in the lungs, and aided in the recovery of pulmonary function. The authors conclude that depositing a vector with the gene that codifies for galectin-3 into the trachea causes blunting of type 2 (Th2) helper T cell effects in rats with allergic lung disease.

Animal models: other challenges and mediators. To define the effect of platelet-activating factor on airway hyperresponsiveness, Nagase and coworkers (59) studied transgenic mice that overexpress the gene for the platelet-activating factor receptor. The transgenic mice displayed greater responsiveness to platelet-activating factor and methacholine than did control mice; responsiveness to serotonin did not differ between the two groups. Atropine blocked the airway responses to platelet-activating factor in the transgenic mice. Airway structure and binding activity of the muscarinic receptor were similar in the transgenic and control mice. The authors conclude that the gene for the platelet-activating factor receptor is involved in airway hyperresponsiveness to methacholine through a functional, but not a structural, mechanism.

Ex vivo studies. The biologic activity of the proinflammatory cytokines, interleukin-13 and interleukin-4, often overlaps. In cultures of human airway smooth muscle cells, Hirst and coworkers (60) studied the capacity of these two cytokines to release eosinophil-activating cytokines. Interleukin-13 and interleukin-4 induced selective release of eotaxin, with no effect on granulocyte-macrophage colony-stimulating factor, RANTES (regu-

lated upon activation, normal T cell expressed and secreted), or interleukin-8. Combining interleukin-13 or interleukin-4 with interleukin-1 β caused marked synergy in the release of eotaxin; a neutralizing antibody to the interleukin-4 receptor α -chain but not to the interleukin-2 γ chain abrogated the effect. Expression of interleukin-4 receptor and interleukin-4 α on the cell surface was constitutive, and did not change when treated with interleukin-13 or interleukin-4 alone or in combination with interleukin-1 β . The activation of interleukin-4 receptor α by interleukin-13 or interleukin-4 induced the activation of transcription-6, p42/p44 ERK, p38, and SAPK/JNK mitogen-activated protein kinase phosphorylation. Activation of transcription-6 and MAP kinase by interleukin-13 or interleukin-4 was not potentiated by interleukin-1 β . The release of eotaxin induced by interleukin-13 or interleukin-4 alone, or in combination with interleukin-1 β , was prevented by an inhibitor of MEK and an inhibitor of p38. The authors conclude that the selective release of eotaxin induced by interleukin-13 and interleukin-4 alone, or in combination with interleukin-1 β , is mediated by interleukin-4 receptor α (which is constitutive on the cell surface) and the activation of multiple intracellular pathways.

Early and late asthmatic responses. To determine whether allergen inhalation causes an increase in the number of bone marrow cells that express protein and messenger RNA for interleukin-5, Wood and coworkers (61) studied 22 patients with asthma (9 displaying isolated early response and 13 dual responders). At 24 hours after an allergen challenge, the dual responders had greater blood and airway eosinophilia than had the early responders. Both groups displayed increases in the percentage of marrow CD3⁺ cells. The percentage of CD3⁺ increased threefold in the dual responders, and doubled in the early responders after the allergen challenge. In the dual responders, allergen induced a 2.6-fold increase in marrow interleukin-5 messenger RNA⁺ cells and a 5.2-fold increase in interleukin-5 messenger RNA⁺ CD3⁺ cells; it had no effect in the early responders. The authors conclude that allergen challenge causes trafficking of T lymphocytes to the bone marrow of patients with atopic asthma, and that dual responders display greater blood and airway eosinophilia and increased ability of bone marrow cells to produce interleukin-5 than do early responders.

Chemical and antigen challenge. To determine whether IgE is synthesized locally in the bronchial mucosa, Wilson and coworkers (62) did bronchoalveolar lavage before and 24 hours after bronchoscopic segmental allergen challenge in 18 patients with atopic asthma. The challenge produced an increase in allergen-specific IgE from 0 to 0.35 μ g per liter. The challenge did not increase allergen-specific IgG; neither did it increase IgE specific to an allergen to which the subject was sensitized but had not been used for provocation. The increase in allergen-specific IgE was still seen after correcting for the effects of dilution and vascular leakage. The authors conclude that allergen provocation causes selective accumulation of allergen-specific IgE within the bronchi, independently of circulating IgE.

To determine whether epithelial cells stimulate myofibroblasts to produce collagen, Hastie and coworkers (63) did segmental antigen challenges in 18 patients with allergic asthma, 4 patients with allergy but no asthma, and 12 healthy subjects. One week after the challenge, the epithelial cells of the patients with asthma had doubled in number, whereas cells from subjects without asthma did not change; proliferation occurred only when the epithelial cells were cocultured with other bronchoalveolar cells. At 1 to 2 weeks after the challenge, human lung fibroblasts showed a 50 to 70% increase in the production of type III collagen (but not of type I collagen) when exposed to factors from the epithelial cells of the asthmatic subjects but not of the subjects without asthma. The authors conclude that allergen

challenge causes the epithelial cells of patients with asthma to proliferate and to stimulate myofibroblasts to produce type III collagen.

De Meer and coworkers (64) studied the determinants of bronchial responsiveness to adenosine 5'-monophosphate (AMP) and methacholine in 230 young adults who were mostly asymptomatic. Bronchial hyperresponsiveness to AMP was associated with prevalence ratios of 2.51 for self-reported allergic rhinitis, 4.38 for self-reported allergic asthma, 3.87 for atopy, and 3.57 for blood eosinophilia; it was not associated with baseline FEV₁. Bronchial hyperresponsiveness to methacholine was inversely related to baseline FEV₁ (prevalence ratio 0.97). The change in slope of the dose response—moving first from control subjects to subjects with rhinitis-conjunctivitis and then to subjects with asthma—was greater for AMP than for methacholine. The authors conclude that bronchial hyperresponsiveness to AMP is determined by allergic background in subjects with mild if any symptoms, whereas bronchial hyperresponsiveness to methacholine is determined by diminished airway caliber. An editorial commentary by Holgate (65) accompanies this article.

To determine whether low-dose allergen exposure can cause asymptomatic airway inflammation, de Kluijver and coworkers (66) did a parallel double-blind trial in 26 patients with house-dust allergy and mild asthma. Inhalation of a low dose of *Dermaphagoides pteronyssinus* on 10 working days caused increases in sputum eosinophils, eosinophilic cationic protein, the ratio of messenger RNA for interleukin-5 to messenger RNA for interferon- γ , and exhaled nitric oxide. Symptoms, peak expiratory flow, and FEV₁ did not change. Inhaled budesonide (400 μ g daily), starting 3 days before allergen inhalation and continued until 7 days after completing allergen inhalation, ameliorated the changes in eosinophilic cationic protein in the sputum, exhaled nitric oxide, and the dose of methacholine inducing a 20% fall in FEV₁. The authors conclude that repeated inhalation of low-dose allergen induces airway inflammation without worsening of symptoms and that the changes can be prevented by inhaled glucocorticoids.

To determine whether acute airway inflammation caused by allergen challenge is increased by subsequent exposure to ozone, Vagaggini and coworkers (67) did a randomized single-blind study in 12 patients with mild atopic asthma. Allergen challenge induced the expected early and late airway responses. Compared with exposure to air, exposure to ozone induced a 14% lower FEV₁, 10% lower FVC, and 18% increase in total symptom score. The percentage of eosinophils in induced sputum was higher after ozone exposure than after air exposure: 27.5 versus 9.9%. The percentage of neutrophils did not differ. The authors conclude that a subsequent exposure to ozone after an allergen challenge potentiates the eosinophilic inflammatory response and airway narrowing in patients with mild asthma.

The enzyme hypothesis has been developed to explain why mite allergens are so strongly associated with the development of allergic responses. Pomes and coworkers (68) determined whether Bla g 2, an allergen produced by the German cockroach (*Blattella germanica*), has enzymatic activity. A molecular model of Bla g 2 had a three-dimensional structure that was similar to that of aspartic proteinases. Critical amino acid substitutions, however, in the catalytic triads and flap region suggested that it was inactive. Experiments confirmed the lack of enzymatic activity. The authors conclude that the allergenicity of the German cockroach allergen, Bla g 2, is not related to enzymatic activity.

Hyperventilation- and exercise-induced asthma. To determine the effect of regular use of inhaled β -agonist therapy on exercise-induced bronchoconstriction and its treatment, Hancox and coworkers (69) did a double-blind crossover trial in eight subjects.

The subjects were randomized to albuterol (200 μ g four times daily) or placebo for one week. After withholding therapy for 8 hours, the subjects performed an exercise challenge known to produce a 15% fall in FEV₁. The fall in FEV₁ after exercise was greater when subjects had been pretreated with albuterol. The response of FEV₁ to treatment with albuterol after exercise was smaller when the subjects had received albuterol during the preceding week. The authors conclude that regular treatment with inhaled β -agonist predisposes to greater bronchoconstriction after exercise and lessens the reversal of the bronchoconstriction with a β -agonist.

Suzuki and Freed (70) studied the effect of inhaled heparin on the late phase of hyperventilation-induced bronchoconstriction in dogs. A dry air challenge to the bronchi produced a 120% increase in peripheral airway resistance at 5 hours, airway hyperreactivity, neutrophilic-eosinophilic inflammation, and increases in leukotriene C₄, leukotriene D₄, leukotriene E₄, and prostaglandin D₂ in bronchoalveolar fluid. Pretreatment with aerosolized heparin attenuated the late-phase airway obstruction by about 50%, abolished airway hyperreactivity, inhibited eosinophil infiltration, and reduced the concentrations of leukotriene C₄, leukotriene D₄, leukotriene E₄, and prostaglandin D₂ in bronchoalveolar fluid. The authors conclude that inhaled heparin inhibits the late phase of airway hyperreactivity induced by hyperventilation in dogs, and that the protection is achieved in part by inhibiting eosinophil migration and the production and release of eicosanoid mediators.

Because the prevalence of lower airway disease is increased in athletes who play sports in cold weather, Davis and coworkers (71) studied elite racing sled dogs at 24 to 48 hours after completing a 1,100-mile endurance race. Of the 59 dogs examined, 81% had abnormal accumulation of debris on bronchoscopy, and 46% had moderate to severe accumulation of exudate. Bronchoalveolar lavage revealed higher nucleated macrophage and eosinophil counts than were seen in control dogs. The authors conclude that strenuous exercise in cold weather causes lower airway disease.

Other Pathophysiological Mechanisms in Asthma

Tachykinins and neural activity. To determine whether inhalation of substance P, a potent agonist of the neurokinin 1 tachykinin receptor, causes microvascular leakage in patients with asthma, Van Rensen and coworkers (72) did a crossover comparison of inhaled substance P versus inhaled neurokinin A (as control) in 12 patients with mild steroid-naive, atopic asthma. Substance P produced increases in markers of microvascular leakage (α_2 -macroglobulin, ceruloplasmin, and albumin) in induced sputum; the increase in leakage was not proportional to the cumulative dose. Inhaled neurokinin A had no effect. The authors conclude that stimulation of the neurokinin 1 receptor with substance P causes a rapid increase in microvascular leakage in the airways of patients with asthma.

Kesler and coworkers (73) studied the effect of noncholinergic parasympathetic nerves on the tone of airway smooth muscle of guinea pigs. The inhibitor of nitric oxide synthase, L-N^G-nitroarginine, and the inhibitor of guanylate cyclase, 1H-[1, 2, 4] oxadiazolo [4, 3-a] quinoxalin-1-one, potentiated cholinergic contractions and partly inhibited noncholinergic relaxations of the trachealis evoked by nerve stimulation. These two inhibitors increased baseline cholinergic tone of the trachealis, and the inhibitor of nitric oxide synthase caused potentiation of contractions of the trachealis induced by histamine. The effects of the nitric oxide synthase inhibitor on the response to histamine were mimicked by vagotomy or selective nerve blockade with tetrodotoxin. Reflex activation of the noncholinergic parasympathetic nerves by bradykinin led to partial reversal of the contractions

of the trachealis induced by histamine. The inhibitor of nitric oxide synthase failed to inhibit this response, and it also did not potentiate the reflex cholinergic contractions of the trachea produced by bradykinin. The authors conclude that noncholinergic parasympathetic nerves modulate the tone of airway smooth muscle.

About a third of vagal afferents innervating the trachea of guinea pigs contain tachykinins, substance P and neurokinin A. Carr and coworkers (74) determined whether viral infections alter the expression of tachykinins in vagal afferents. On exposure to a vehicle, about 3% of neurons in the trachea of guinea pigs stained positively for substance P or neurokinin A. The cell bodies of these neurons had a small diameter, a feature of nociceptive-like C fibers. Infection with Sendai virus increased the number of neurons containing substance P or neurokinin A to about 20% of total neurons on the fourth day. Most of the cell bodies had large diameters, a feature of nonnociceptive afferent neurons. The induction was reversible, decreasing by 28 days after inoculation with the virus. The authors conclude that viral infection in guinea pigs induces qualitative changes in vagal afferent innervation of guinea pig airways such that both small diameter nociceptive-like neurons and large diameter nonnociceptive neurons express tachykinins.

Postganglionic parasympathetic nerves mediate both cholinergic contractions and nonadrenergic, noncholinergic relaxations of smooth muscle in the airway. Mazzone and Canning (75) studied the different regulation of contractile and relaxation reflexes of these two pathways in guinea pigs. Pronounced contractile and relaxant parasympathetic reflex responses could be evoked by intravenous histamine, application of capsaicin to the laryngeal mucosa, or electrical stimulation of vagal afferents projecting from the abdominal viscera. These data suggest that activation of multiple vagal afferent subtypes can initiate both cholinergic and noncholinergic parasympathetic reflexes in the airways. All of the contractile and relaxant responses evoked by these stimuli were absent in vagotomized animals or in animals pretreated with the ganglionic blocker, trimethaphan, confirming their reflex and parasympathetic nature. The authors conclude that cholinergic and noncholinergic parasympathetic nerves that regulate airway caliber in guinea pigs consist of two distinct parasympathetic pathways that are subject to differential reflex inhibition.

Calcitonin gene-related peptide is colocalized with substance P in sensory C-fiber afferents in the airways. Dakhama and coworkers (76) studied the effects of sensitization and exposure to allergen on the expression of this peptide. In mice sensitized to ovalbumin, aerosol challenge with ovalbumin induced eosinophilic inflammation of the airways, airway hyperresponsiveness, and considerable depletion of calcitonin gene-related peptide in neuroepithelial bodies and submucosal nerve plexuses. Aerosol challenge did not change the overall density of nerve fibers in the airways. Treatment with antibodies against very late antigen-4 and interleukin-5 blocked the airway eosinophilia and hyperresponsiveness, and prevented depletion of the peptide. In sensitized and challenged mice, administration of calcitonin gene-related peptide caused normalization of the airway response to methacholine. The authors conclude that allergen exposure depletes calcitonin gene-related peptide in neuroepithelial bodies and submucosal nerve fibers, and that replacement of the peptide can reverse the changes in airway responsiveness.

Neuropeptides, especially substance P, are found in the lungs of patients with asthma, and production is increased by nerve growth factor. To determine the role of nerve growth factor in the early allergic reaction, Path and coworkers (77) challenged ovalbumin-sensitized mice with inhaled ovalbumin. Antibodies to nerve growth factor inhibited the early-phase response to

inhaled allergen and suppressed airway inflammation. Compared with wild-type mice, sensitization and challenge of transgenic mice that constitutively overexpress the nerve growth factor in their airways displayed increases in the early-phase reaction and airway inflammation. The levels of serotonin in the airways were increased, whereas immunoglobulin E was unaffected. The transgenic mice displayed increased reactivity of sensory nerves in response to inhaled capsaicin, demonstrating that the nerve growth factor mediates neuronal plasticity. The authors conclude that nerve growth factor contributes to the early phase reaction to allergen.

Neurogenic inflammation in the bronchi is thought to involve continuous pathways between sensory nerve endings in the epithelium and blood vessels in the mucosa. Using immunofluorescent staining and confocal microscopy in whole mounts of mucosa from pigs and humans, Lamb and Sparrow (78) tried to find structural evidence of the pathway for the axon reflex. An extensive plexus of nerves was found in the apical and basal epithelium; 94% of the nerves were varicose fibers that were immunoreactive for substance P. The varicose apical processes followed closely around the circumference of goblet cells. In the varicosities, calcitonin gene-related peptide was colocalized with the fibers that were immunoreactive for substance P. As the fibers entered the lamina propria, they converged into bundles, and lateral branches ran along arterioles. Substance P-immunoreactive fibers were rare near postcapillary venules. The authors conclude that the tracing of individual nerve fibers demonstrate a continuous pathway that provides a structural basis for the local axon reflex involved in the vasodilation of neurogenic inflammation.

Remodeling. To determine the effect of age on allergen-induced airway inflammation and remodeling, Palmans and coworkers (79) studied rats of 2 weeks and 13 weeks of age. The rats were sensitized to aerosolized ovalbumin for 2 weeks at 4 weeks of age. Compared with saline-treated rats, both groups of ovalbumin-treated rats developed greater inflammatory and structural changes. Compared with the older rats, the young rats displayed a 76% increase in peribronchial eosinophils, an 88% increase in goblet cell hyperplasia, and a 48% increase in the area of fibronectin deposition in the airway wall. The authors conclude that young rats are more susceptible to allergen-induced inflammatory and structural changes in the airways than are older rats.

To define the prevalence and risk factors for airway remodeling, Rasmussen and coworkers (80) studied a birth cohort of 1,037 children followed longitudinally to age 26 years. Remodeling was defined functionally as a postbronchodilator FEV₁/FVC ratio below the normal range; the lower limit of the normal ratio was defined as the mean ratio in healthy subjects minus 1.96 standard deviations. Postbronchodilator FEV₁/FVC was below the normal range in 7.4% of the cohort at 18 years and 6.4% at 26 years. Subjects with a consistently low postbronchodilator FEV₁/FVC ratio had a greater decline in the prebronchodilator FEV₁/FVC ratio between ages 9 and 26 years than did subjects with a normal postbronchodilator FEV₁/FVC ratio: -12% versus -6% in male subjects and -10.5% versus -5.5% in female subjects. Asthma, male sex, airway hyperresponsiveness, and low lung function in childhood were each independently associated with a low postbronchodilator FEV₁/VC ratio, which in turn was associated with accelerated decline in lung function. The authors conclude that airway remodeling in asthma begins in childhood and continues into adult life. An editorial commentary by von Mutius (81) accompanies this article.

The excessive airway narrowing in patients with asthma is thought to result from airway remodeling. In samples of both large and small airways from five patients who died from asthma,

five patients with asthma who died from nonrespiratory causes, and five control subjects without asthma, James and coworkers (82) studied the relationship between thickness of the reticular basement membrane and the dimensions of the airway wall. In large cartilaginous airways, thickness of the reticular basement membrane was correlated with the percentage of smooth muscle ($r = 0.51$) and the percentage of inner wall area ($r = 0.55$). In small cartilaginous airways, thickness of the reticular basement membrane was correlated with the percentage of smooth muscle ($r = 0.30$) and the percentage of inner wall area ($r = 0.58$). Equivalent relationships were not observed for the membranous airways. The authors conclude that the thickening of the reticular basement membrane of the central airways is correlated with airway remodeling in the cartilaginous airways, but it is not correlated with wall dimensions of the membranous airways.

Airway inflammation and remodeling in chronic asthma are characterized by airway eosinophilia, hyperplasia of goblet cells and smooth muscle, and subepithelial fibrosis. To investigate the role of leukotrienes in this process, Henderson and coworkers (83) developed a model of chronic lung inflammation and fibrosis. Mice were sensitized by intraperitoneal administration of ovalbumin on Days 0 and 14, and ovalbumin was administered periodically through the nose between Day 14 and Day 75. The mice developed extensive eosinophil and mononuclear cell inflammation, goblet cell hyperplasia, and mucus occlusion of the airways. The ovalbumin-treated mice, but not the control mice, displayed widespread deposition of collagen beneath the airway epithelial cell layer and in the interstitium at sites of leukocytic infiltration. In the ovalbumin-treated mice, montelukast, an antagonist of the cysteinyl leukotriene₁ receptor, reduced the airway eosinophil infiltration, mucus plugging, smooth muscle hyperplasia, subepithelial fibrosis, Charcot-Leyden-like crystals in airway macrophages, and the increase in expression of messenger RNA for interleukin-4 and interleukin-13. The authors conclude that cysteinyl leukotrienes play an important role in airway inflammation and fibrosis resulting from exposure to allergen.

In a rat model of airway remodeling, inhaled glucocorticoids have been shown to partly prevent the development of structural changes in the airway caused by allergen. Vanacker and coworkers (84) determined whether the combination of inhaled salmeterol plus fluticasone propionate would prevent further progression of already established airway remodeling. Airway remodeling was induced in sensitized rats by exposing them to ovalbumin every second day between Days 14 and 28. The rats were then exposed to a further 14 days of ovalbumin or placebo. Four weeks of exposure to ovalbumin produced airway inflammation, goblet cell hyperplasia, and enhanced deposition of fibronectin and collagen. On its own, salmeterol decreased the number of eosinophils in bronchoalveolar fluid, but it had no effect on the structural changes. The combination of salmeterol and fluticasone counteracted the goblet cell hyperplasia, but it increased the amount of fibronectin and collagen in the airway wall. Salmeterol did not influence airway responsiveness. The authors conclude that the combination of salmeterol and fluticasone propionate enhances aspects of airway remodeling caused by inhaled allergen, but it does not alter airway responsiveness.

Treatment

β-Agonists. To determine whether administering nebulized albuterol in conjunction with a low-density gas, helium–oxygen, would improve lung function, Kress and coworkers (85) randomized 45 patients to albuterol combined with helium–oxygen versus albuterol combined with oxygen. The patients with acute severe asthma (FEV_1 , 32% predicted) received three consecutive treatments. Compared with the control group, the median increase in FEV_1 was higher in the helium–oxygen group after the

first albuterol treatment, 32.4 versus 14.6%, second albuterol treatment, 51.5 versus 22.7%, and third albuterol treatment, 65.1 versus 26.6%. The authors conclude that nebulized albuterol combined with helium–oxygen achieves greater bronchodilation than does albuterol combined with oxygen in patients with acute severe asthma.

In a pulmonary perspective, Hanania and colleagues (86) discuss the measurement and clinical significance of the intrinsic efficacy of β -agonists.

Inhaled glucocorticoids. 11β -Hydroxysteroid dehydrogenase type II acts on natural glucocorticoids to produce inactive metabolites. To determine whether this enzyme is found in the human airway, Orsida and coworkers (87) did airway biopsies in 15 patients with asthma being treated with inhaled glucocorticoids, 7 patients with asthma not receiving inhaled glucocorticoids, and 9 subjects without asthma. Immunoreactivity for the enzyme was generally localized to the endothelium of vessels in the lamina propria and airway epithelium in both the patients with asthma and in the subjects without asthma. The extent of staining for the enzyme was inversely correlated with the dose of inhaled glucocorticoid required for effective treatment ($r = -0.44$); this finding suggests that the enzyme aids in the regeneration rather than in the breakdown of glucocorticoids. The authors conclude that 11β -hydroxysteroid dehydrogenase type II is found in the human airway and the level of the enzyme is inversely related to the dose of inhaled glucocorticoids needed to control asthma.

The dose of an inhaled glucocorticoid usually consists of an arbitrary number of micrograms. To develop a reliable method for evaluating systemic bioavailability, Martin and coworkers (88) compared the action of 6 inhaled glucocorticoids with matching placebo in 165 patients with asthma. The systemic action was assessed by hourly levels of plasma cortisol between 8:00 P.M. and 8:00 A.M., 12-hour and 24-hour urinary concentrations of cortisol, and morning blood osteocalcin. The area under the concentration–time curve for hourly concentrations of cortisol was the best outcome measure. The microgram comparison for cortisol suppression of 10% were: flunisolide–chlorofluorocarbon, 936 mcg; triamcinolone–chlorofluorocarbon, 787 mcg; beclomethasone–chlorofluorocarbon, 548 mcg; fluticasone dry powder inhaler, 445 mcg; budesonide dry powder inhaler, 268 mcg; and fluticasone–chlorofluorocarbon, 111 mcg. The authors conclude that the described cortisol suppression test provides a first step in the comparison of inhaled glucocorticoids based on an efficacy of doses rather than an arbitrary dosage.

Inhalation of allergen induces the expansion of eosinophil progenitors in the bone marrow of patients with asthma, and inhaled glucocorticoids decrease the baseline number of eosinophil/basophil progenitors. In ovalbumin-sensitized mice, Shen and coworkers (89) determined whether inhaled budesonide ameliorates allergen-induced airway inflammation by preventing hematopoietic cytokine release. Budesonide attenuated the eosinophilia in bone marrow, peripheral blood, and the airways in response to allergen inhalation, and it attenuated the increase in eosinophil progenitors in the bone marrow. At 12 hours after the second of two daily exposures to allergen, budesonide did not prevent the increases in interleukin-5 or eotaxin. Budesonide attenuated interleukin-5, eosinophilia, bone marrow eosinophil/basophil progenitors, and airway hyperresponsiveness at a later time. The authors conclude that glucocorticoids attenuate allergen-induced airway inflammation in part through suppression of the increase in eosinophil progenitors in the bone marrow, rather than by simply blocking production of interleukin-5 at the airway.

To determine whether the use of inhaled glucocorticoids is associated with the development of a hip fracture, Hubbard and coworkers (90) did a case-control study of 16,341 cases of hip

fracture in a general practice research database and 29,889 control subjects. After adjusting for potential confounders, conditional logistic regression revealed an association between hip fracture and inhaled glucocorticoids (odds ratio, 1.26). After adjusting for annual courses of oral glucocorticoids, the odds ratio was reduced to 1.19. Hip fractures displayed a dose-response relationship to inhaled glucocorticoids. The authors conclude that use of inhaled glucocorticoids is associated with the development of hip fracture in older subjects.

Glucocorticoids. To determine the relationship between use of glucocorticoids, bone mineral density, and fracture, Walsh and coworkers (91) studied patients who had taken continuous or frequent courses of oral glucocorticoids for asthma, COPD, or idiopathic pulmonary fibrosis over the preceding six months. Of 117 patients, 48% were women, 58% had osteoporosis, and 61% had a vertebral fracture. The presence of a vertebral fracture was related to bone mineral density of the femoral neck (measured by X-ray absorptiometry): odds ratio was 1.6 for a reduction of 1 SD in density. Between the highest and lowest quartile dose of prednisolone, the risk of vertebral fracture increased 4.4-fold; adding bone density of the femoral neck did not alter the relationship. The authors conclude the risk of vertebral fracture is strongly related to the cumulative dose of prednisolone, and that this effect is independent of its more modest effect on bone mineral density.

Leukotriene inhibitors. In sheep with airway hyperreactivity to *Ascaris suum*, Sabater and coworkers (92) determined whether montelukast, a cysteinyl leukotriene₁-receptor antagonist, could prevent or reverse antigen-induced mucociliary dysfunction. Eight hours after antigen challenge, tracheal mucus velocity had decreased to 56% of the baseline value. The decrease in mucus velocity was prevented by pretreatment with montelukast. Administration of montelukast at either 1 hour or 4 hours after the antigen challenge neither prevented nor reversed the decrease in mucus velocity. The authors conclude that the early release of cysteinyl leukotrienes contributes to the fall in tracheal mucus velocity that follows antigen challenge and that pretreatment with montelukast reduces this impairment.

Combination regimens. In a double-blind randomized trial, Dahlen and coworkers (93) assessed the benefit of adding a leukotriene antagonist, montelukast 10 mg, in the management of 80 aspirin-intolerant patients with asthma; 90% of the patients were being treated with moderate or high doses of glucocorticoids. Compared with placebo, 4 weeks of montelukast produced an increase in FEV₁ of 10%, an increase in morning PEF_R of 28 liters per minute, a decrease in use of bronchodilator medication of 27%, a decrease in asthma exacerbations of 54%, an increase in the quality of life, and 1.3 more nights of sleep a week. The therapeutic response did not correlate with the baseline level of urinary leukotriene E₄. The authors conclude that montelukast produces benefit over and above that achieved by glucocorticoids in aspirin-intolerant patients with asthma.

To determine whether the combination of inhaled budesonide (400 µg for 10 days) and a leukotriene receptor antagonist, montelukast (10 mg daily for 10 days) provides greater anti-inflammatory effects than either agent alone, Leigh and coworkers (94) did a randomized, double-blind crossover study in 10 patients with mild asthma (FEV₁, 82% predicted). Inhalation of allergen produced a maximal early fall in FEV₁ of 28% after placebo, 25% after budesonide, 12% after montelukast, and 11% after the combination. The maximal late fall in FEV₁ after allergen inhalation was 18% after placebo, 3% after budesonide, 8% after montelukast, and 3% after the combination. Airway hyperresponsiveness consequent to inhaled allergen was reduced by budesonide, montelukast, and the combination; the effect of budesonide was greater than that of montelukast. Sputum

eosinophilia induced by inhaled allergen was attenuated by budesonide, montelukast, and the combination. The authors conclude that bronchoconstriction, airway hyperresponsiveness, and sputum eosinophilia secondary to inhaled allergen are attenuated by either budesonide or montelukast, but that the combination of budesonide and montelukast does not have a greater effect than either drug on its own.

Immunotherapy. To determine whether avoiding exposure to house dust mite allergen influences the development of symptoms in the first two years of life, Koopman and coworkers (95) selected 1,282 pregnant women with allergy. Of the women, 416 were randomized to receive mattress covers that were impermeable to house-dust mite allergen for the beds of the children and the parents, 394 received placebo covers, and 472 received no intervention. Compared with individuals who received placebo covers, children in the group that received active covers had a lower prevalence of night cough without a cold in the second year of life (odds ratio, 0.65). The intervention had no effect on other respiratory symptoms, atopic dermatitis, or total and specific IgE. The authors conclude that applying a mattress cover that is impermeable to house-dust mite allergen on the beds of children and their parents reduces night cough in the second year of life.

Management plans and education. To determine whether a self-management program for adults with asthma provides efficient management, Schermer and coworkers (96) recruited 193 patients being managed by family practitioners and randomized them into a self-management program, a usual care program, and monitored them for 2 years. The gain of quality-adjusted life years was 0.039 for the self-managed patients and 0.024 for the usual care patients. Over the 2 years, self-managed patients experienced 81 successfully treated weeks and usual care patients experienced 75 successfully treated weeks. Total costs were €1,084 for the self-managed patients and €1,097 for usual care patients. The self-managed patients consumed 1,680 puffs of budesonide and the usual care patients consumed 1,897 puffs. Cost of mean productivity caused by days of impaired activity was €213 lower among the self-managed patients. The authors conclude that self-management of asthma is safe and efficient as compared with the usual care provided by family practitioners.

To determine whether an index based on the type and daily amount of medication could serve as a proxy for the severity of asthma, Ungar and coworkers (97) analyzed data from 1,279 adults with asthma or parents of children with asthma participating in a community surveillance program. Adults with greater use of medications had more frequent physician visits, pulmonary function tests, and hospital admissions. The findings were similar among children. The use of medications was weakly correlated with the frequency of symptoms, an indicator of disease control. The authors conclude that an index based on the use of medications may serve as a proxy for severity of asthma in population-based research.

To determine whether a brief, self-administered questionnaire would predict utilization of health-care resources, Vollmer and coworkers (98) studied 4,795 adult members of a health maintenance organization. The subjects completed the questionnaire in the fall of 1997, and the investigators recorded health care utilization throughout 1998. Compared with subjects who had no control problems, the relative rates of acute care episodes were 3.5 for subjects who had 3 to 4 control problems, 1.7 for subjects who had 2 control problems, and 1.4 for subjects who had 1 control problem. The authors conclude that an asthma-control index, derived from a self-administered questionnaire, predicted the utilization of health care resources over the ensuing year.

Specific Clinical Scenarios

Nocturnal asthma. Landstra and coworkers (99) asked the question, "Does serum cortisol contribute to nocturnal airway obstruction?" In 18 children with asthma but free of nocturnal worsening of asthma, serum cortisol was lower at midnight than in 18 healthy children. In 10 children with nocturnal asthma (24-hour variation in FEV₁ of at least 15%), serum cortisol was lower at midnight, 8:00 A.M., and midday than in the healthy subjects. A low level of cortisol over the 24-hour period was associated with a lower FEV₁ at 4:00 A.M., 8:00 A.M., and 8:00 P.M. in the patients with asthma, but not in the healthy subjects. Greater variation in the level of cortisol over 24 hours was associated with a lower FEV₁ at all time points in the healthy children and in the children who had asthma but were free of nocturnal asthma. Variation in serum cortisol was not related to blood eosinophils or to bronchial hyperresponsiveness to methacholine or adenosine. The authors conclude that lower serum levels of cortisol contribute to airway obstruction, especially at night.

To determine whether melatonin, a regulator of circadian rhythm, alters the inflammatory characteristics of peripheral blood mononuclear cells, Sutherland and coworkers (100) performed phlebotomy and spirometry at 4:00 P.M. and 4:00 A.M. in 6 patients with nocturnal asthma, 12 patients with asthma that was not nocturnal, and 5 healthy subjects. In all groups, the addition of melatonin to zymosan-stimulated mononuclear cells caused increased production of interleukin-1, interleukin-6, and tumor necrosis factor- α at both time points (range, 13 to 132%). In the healthy subjects, the increase in cytokines in response to melatonin was small at 4:00 P.M. (14 to 21%), and the response was not greater at 4:00 A.M. (with the exception of interleukin-6). In the patients with non-nocturnal asthma, the response to melatonin at 4:00 P.M. was similar to that seen in the healthy subjects, but the response at 4:00 A.M. was markedly greater. The patients with nocturnal asthma had a heightened response to melatonin at both 4:00 P.M. and 4:00 A.M., with no difference between the two time points. The authors conclude that melatonin is proinflammatory both in patients with asthma and in healthy subjects, and that the daytime cytokine response is greatest in patients with nocturnal asthma and it does not increase further in these patients at 4:00 A.M.

Gastroesophageal reflux. In eight patients with intermittent asthma and eight healthy subjects, Zerbib and coworkers (101) studied the effect of a methacholine challenge on motility of the lower esophageal sphincter and the occurrence of gastroesophageal reflux. In the healthy subjects, methacholine (2 mg) did not induce a decrease in FEV₁, and did not alter esophageal pH or motility of the lower esophageal sphincter. In the patients with asthma, methacholine induced a 22% decrease in FEV₁, an increase in the number of reflux episodes (0.8 versus 0.3 per 30 minutes), and an increase in the rate of transient relaxations of the lower esophageal sphincter (3.5 versus 1.0 per 30 minutes). Inhalation of albuterol did not change the number of reflux episodes (1.0 per 30 minutes) but it decreased the rate of relaxations of the lower esophageal sphincter (1.6 per 30 minutes) in the patients with asthma. The authors conclude that the induction of bronchial obstruction increases the rate of relaxations of the lower esophageal sphincter and episodes of reflux in patients with asthma, and that albuterol decreases the rate of the relaxations.

Dyspnea. The ability to sense bronchoconstriction may be modulated by airway inflammation. Salome and coworkers (102) addressed this issue in 35 patients with asthma by studying the effect of inhaled budesonide on the perception of airway narrowing induced by inhaled histamine. After 8 weeks of inhaled

budesonide, the slope of the relationship between breathlessness (Borg score) and percent fall in FEV₁ was 66% greater than was the slope at baseline. The increase in the slope was not related to baseline FEV₁, airway hyperresponsiveness, blood eosinophils, serum eosinophil cationic protein, previous treatment with inhaled glucocorticoids, or the dose of budesonide. The authors conclude that an inhaled glucocorticoid enhances the perception of airway narrowing in patients with asthma.

The respiratory sensation of increased effort to breathe occurs with many respiratory disorders, but the sensation of chest tightness is unique to bronchoconstriction. To determine whether tightness is related to work of breathing, Binks and coworkers (103) used methacholine to induce a 16% decrease in the FEV₁/FVC ratio in 15 subjects with mild asthma. Methacholine produced sensations of both increased effort and tightness in all subjects. Mechanical ventilation produced a 16% decrease in the sense of effort, but it did not significantly reduce the sense of tightness as compared with spontaneous breathing. An increase in end-expiratory volume of 279 ml occurred with methacholine; an equivalent increase in end-expiratory volume, induced by positive end-expiratory pressure, did not produce increased effort or tightness. The authors conclude that an increase in respiratory work contributes to the sense of effort, but not to the sense of chest tightness that accompanies acute bronchoconstriction in patients with asthma. An editorial commentary by Davenport (104) accompanies this article.

Failure to recognize the severity of an attack of asthma is associated with asthma deaths. To determine whether patients with asthma have problems in processing perceptual information, Webster and Colrain (105) studied respiratory and auditory evoked responses in 16 patients with asthma and 16 healthy subjects. On breathing against four resistive loads, magnitude estimation on a modified Borg scale was linearly related to the intensity of the resistive load in both the patients ($r^2 = 0.96$) and the control subjects ($r^2 = 0.99$). Respiratory-related evoked potentials were measured with scalp encephalograms in response to inspiratory occlusions of 200-millisecond duration. P3 (the amplitude at 250 to 350 milliseconds after the change in mouth pressure) was smaller in the patients with asthma than in the control subjects: 16.9 versus 22.9 μ V. The P3 component of the evoked potential in response to auditory signals was also lower in the patients than in the control subjects: 13.2 versus 18.6 μ V. The authors conclude that patients with asthma have an impaired capacity for perceptual processing of respiratory and auditory information.

Cough. Because more women than men attend specialist cough clinics, Kastelik and coworkers (106) compared the sensitivity of the cough reflex in 60 female and 50 male patients with chronic cough. The dose of inhaled capsaicin inducing two coughs was 2.2 times smaller and the dose inducing five coughs was 6 times smaller in the women than in the men. The dose of inhaled citric acid inducing cough was 2.2 times smaller and the dose inducing five coughs was 2.8 times smaller in the women than in the men. The authors conclude that female patients with chronic cough displayed greater sensitivity to cough than do male patients.

In a clinical commentary, Irwin and Madison (107) discuss persistently troublesome cough.

Psychopathology. Liu and coworkers (108) asked the question, "Does psychological stress alter the inflammation of the airways caused by antigen challenge?" On questionnaires, 20 college students with mild asthma had higher scores for anxiety and depression during the week of final examination than they did during the middle of a semester. An inhaled challenge with allergen induced higher levels of sputum eosinophils and eosinophil-derived neurotoxin at 6 and 24 hours after the challenge

during the period of stress. The level of interleukin-5 produced by sputum cells in response to stimulation with phytohemagglutinin was increased at 24 hours during stress and was related to the number of sputum eosinophils ($r = 0.65$). The authors conclude that psychological stress enhances the eosinophilic inflammatory response to inhaled allergen. An editorial commentary by Bienenstock (109) accompanies this article.

Occupational Asthma

Diisocyanates. Peripheral blood monocytes of patients with diisocyanate asthma produce monocyte chemoattractant protein-1 in response to diisocyanate human serum albumin. To determine the diagnostic usefulness of this response, Bernstein and coworkers (110) studied 54 workers exposed to diisocyanate. A diagnosis of diisocyanate asthma was confirmed by a specific inhalation challenge in 19 (35%) of the workers. The assay for production of monocyte chemoattractant protein-1 (in response to diisocyanate-human serum albumin) had a diagnostic sensitivity of 79% and a specificity of 91%. Diisocyanate-specific IgG had a sensitivity of 47% and a specificity of 74%. Diisocyanate-specific IgE had a sensitivity of 21% and a specificity of 89%. The authors conclude that an *in vitro* assay for production of chemoattractant protein-1 in response to diisocyanate-human serum albumin is superior to specific IgE and IgG antibodies in the diagnosis of diisocyanate asthma. An editorial commentary by Hendrick (111) accompanies this article.

Farmers. To determine the prevalence of sensitization to allergens in the workplace and the prevalence of occupational asthma among growers of greenhouse flowers or ornamental plants, Monso and coworkers (112) studied 39 growers. Thirteen of 38 growers (34%) were sensitized to flowers or molds, but sensitization was not related to characteristics of the greenhouses. Poor ventilation was a marginal risk factor for wheezing. Occupational asthma was confirmed by bronchial provocation in three workers (7.7%), all of whom were sensitized to workhouse flowers or molds. None of the nonsensitized workers had occupational asthma. The authors conclude that occupational asthma occurs in 8% of growers of greenhouse flowers, ornamental plants, or both, and in a quarter of workers sensitized to flowers or molds.

Prevalence and severity. To determine the influence of occupational exposure on the incidence of respiratory symptoms and asthma, Egan and coworkers (113) undertook an 11-year community cohort study in 2,819 Norwegian subjects. At baseline, the prevalence of exposure to quartz was 3.7%, to asbestos 5.0%, and to dust or fumes 28.3%. After adjusting for sex, age, educational level, and smoking, the odds ratios for the development of respiratory symptoms or asthma in subjects exposed to dust or fumes varied between 1.4 and 2.1. After adjusting for the confounding variables, 14% of the incidence of asthma and 6 to 19% of the incidence of respiratory symptoms were attributable to exposure to dust or fumes. The authors conclude that airborne occupational exposure increases the incidence of asthma and respiratory symptoms.

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