

ASTHMA AND ALLERGIC DISEASES

Allergies are the result of inappropriate immune responses to normally harmless substances. Allergy symptoms vary widely, from the sneezing, watery eyes, and nasal congestion of mild “hay fever” to severe rashes, swelling, and shock. Asthma is a chronic inflammation of the lungs that airborne allergens can trigger in susceptible people; tobacco smoke, air pollution, viral respiratory infections, or strenuous exercise can also contribute. Asthma and allergic diseases can significantly decrease quality of life, employee productivity, and school attendance; in severe cases, they can be life-threatening. The goal of NIAID’s asthma and allergic diseases research program is to develop more effective treatments and prevention strategies.

Allergies are the sixth leading cause of chronic disease in the United States and cost the healthcare system \$18 billion annually.¹⁹ About half of all Americans test positive for at least one of the 10 most common allergens (ragweed, Bermuda grass, rye grass, white oak, Russian thistle, *Alternaria* mold, cat, house dust mite, German cockroach, and peanut),²⁰ and about 50 million suffer from allergic diseases each year. Food allergy occurs in 6 to 8 percent of children aged six years or younger and in 2 percent of adults.²¹ Common food allergens include cow’s milk, eggs, shellfish, and nuts; peanuts and tree nuts are the leading causes of fatal and near-fatal food allergy reactions.

The prevalence of asthma is also high. In 2005, 30 million people living in the United States had asthma, resulting in more than 480,000 hospitalizations and approximately 4,200 deaths. African Americans are disproportionately affected by asthma. In 2002, the asthma prevalence among non-Hispanic African Americans was approximately 30 percent higher than among non-Hispanic whites, and approximately double the level among Hispanics. Non-Hispanic African Americans had an asthma

attack prevalence about 30 percent higher than that of non-Hispanic whites, and almost 77 percent higher than Hispanics. Among individual race/ethnic groups, Puerto Ricans have the highest levels of asthma prevalence and asthma attack prevalence. For reasons that are still unclear, the prevalence of both allergy and asthma in the United States is increasing.

The causes, pathogenesis, diagnosis, treatment, and prevention of asthma and allergic diseases are major areas of emphasis for NIAID’s Division of Allergy, Immunology, and Transplantation. NIAID vigorously pursues research on asthma and allergic diseases by supporting investigator-initiated projects, cooperative clinical studies, a national network of research centers, and demonstration and education research projects.

In fiscal year (FY) 2005, NIAID established the Food Allergy Research Consortium, a collaborative research program designed to develop new approaches to treat and prevent food allergy. The consortium will conduct basic, clinical, and epidemiological studies, and develop educational programs aimed at parents, children, and healthcare providers. The program goals are to develop immune intervention strategies for preventing and treating food allergy; identify the mechanisms of development, loss, and re-emergence of oral tolerance; determine the molecular and functional characteristics of food allergens; and determine the role of the gastrointestinal tract in development and loss of oral tolerance. The consortium’s first project is a study of the development of and loss of tolerance to foods in a cohort of high-risk children. Its second project is a clinical trial to evaluate a potential therapy for peanut allergy.

The Inner-City Asthma Study, cofunded by NIAID and the National Institute of Environmental and Health Sciences (NIEHS), was a multicenter, randomized controlled trial that tested the effectiveness of two interventions in reducing asthma morbidity among inner-

city children with moderate to severe asthma. The study concluded in 2001. One intervention provided physicians with more detailed and up-to-date information on participants' recent asthma symptoms and medication use. The other intervention reduced exposure to environmental triggers such as tobacco smoke, allergens derived from cockroaches, house dust mite, mold, furry pets, and rodents. Participants were evaluated during both the 1-year intervention period and a 1-year followup period. The study included 937 children between the ages of 5–10 years, from seven inner cities. The environmental intervention decreased exposure to indoor allergens, including cockroach and house dust mite and tobacco smoke, resulting in reduced asthma associated morbidity.²² The physician feedback letter resulted in no change in symptoms, but a 24 percent reduction in emergency room visits.²³

One project within the Inner-City Asthma Study evaluated the impact of indoor and outdoor fine particles and co-pollutants on respiratory illnesses. Recently published data from this study, which was funded by NIAID, NIEHS, and the U.S. Environmental Protection Agency, demonstrate that approximately 25 percent of indoor particle concentration is contributed by outdoor particles. These data also show that smoking is the major source of indoor particles and that indoor concentrations of fine particles peak in the late evening in homes where smoking occurs, perhaps reflecting the influence of after-dinner smoking. Analysis of data pertaining to the effects of particle concentrations on asthma symptoms is currently underway.

The Inner-City Asthma Consortium (ICAC) is a NIAID-funded research network that evaluates the safety and efficacy of immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children, investigates the mechanisms of action of the immune-based therapies, develops and validates biomarkers of disease progression, and investigates the immunopathogenesis of asthma in inner-city

children. Current studies include an Asthma Control Evaluation, a randomized prospective study to evaluate the use of measurement of exhaled nitric oxide, which increases during periods of uncontrolled asthma, as a surrogate marker for asthma worsening; the Urban Environmental Factors and Childhood Asthma study, a longitudinal prospective study in inner-city children of the immunologic causes of the development of recurrent wheezing, including evaluation of cytokine response patterns; and the Inner-City Anti-IgE Therapy for Asthma trial, a randomized, double-blinded, placebo-controlled, parallel group, multicenter trial to evaluate the safety and efficacy of Xolair (omalizumab) in inner-city children with moderate to severe allergic asthma whose symptoms are inadequately controlled with inhaled steroids. The ICAC has completed an ancillary study, the German Cockroach Allergen Standardization Evaluation.

NIAID supports 13 Asthma and Allergic Diseases Research Centers (AADRCs), which are the cornerstone of the pathobiology component of the NIAID asthma and allergy research portfolio. The AADRCs conduct basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma and allergic diseases.

NIAID and the National Heart, Lung, and Blood Institute (NHLBI) cosponsor the Immune System Development and the Genesis of Asthma program, which supports research on changes in immune function that occur early in life and lead to the development of asthma. Identification of the cellular and molecular processes involved in the onset of asthma will provide the basis for devising novel and effective new immune-based strategies for asthma treatment and prevention that do not compromise the integrity of the immune system. NIAID supports seven research projects through this program and NHLBI supports six projects.

The Immune Tolerance Network (ITN) is an international consortium of basic scientists and clinical investigators that performs clinical research to evaluate the safety and efficacy of methods that can induce the immune system to tolerate certain antigens, including allergens, for the treatment of immune-mediated disorders. The ITN, which is co-sponsored by NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Juvenile Diabetes Research Foundation International, has completed a trial of recombinant ragweed allergen-immunostimulatory DNA conjugates for the treatment of allergic rhinitis. Preliminary data suggest that this conjugate, when given to ragweed allergic patients prior to the ragweed season, reduced symptoms in both that year's and the following year's ragweed season. The ITN is conducting a trial to determine the efficacy of the combination of anti-IgE (omalizumab) and ragweed allergen immunotherapy for treatment of allergic rhinitis and is also developing three other allergy protocols. These include recombinant ragweed allergen-immunostimulatory DNA conjugates in asthma; asthma/allergy prevention in young children by oral mucosal immunotherapy with house dust mite, cat, and timothy grass; and peanut allergy prevention by oral administration, in infants, of bamba, a peanut butter snack.

More information on ITN is available at www.immunetolerance.org.

In FY 2004, NIAID established the Atopic Dermatitis and Vaccinia Network to develop short- and long-term approaches to reduce the incidence and severity of eczema vaccinatum, and protect individuals with atopic dermatitis from adverse consequences of vaccinia exposure.

An important NIAID intramural study is examining how allergen immunotherapy (AIT) reduces or prevents reactions to allergens such as pollen, dust, or cat dander. Although the efficacy of AIT in asthma is modest, it is nonetheless the only disease-modifying therapy for allergic asthma currently known. Certain types of white blood cells, called Th2 cells, produce substances that contribute to the development of allergies, while others, called Th1 cells, produce substances that can inhibit the development of allergies. This study will determine whether AIT changes the immune response to allergens by reducing the number of Th2 cells or by converting them into Th1 cells. A better understanding of the mechanisms underlying the clinical effectiveness of AIT might help scientists to discover new approaches to treating allergies and asthma.