

Asthma in the inner city: The perspective of the National Institute of Allergy and Infectious Diseases

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Since 1991, the National Institute of Allergy and Infectious Diseases (NIAID) has funded four consecutive research initiatives to investigate the problem of high asthma prevalence, morbidity and mortality in poor urban communities. The multi-site studies conducted under these initiatives have identified key risk factors for asthma morbidity and novel interventions to improve asthma control. NIAID focuses its asthma and allergy programs on understanding the interaction of the immune system with allergens and infectious agents and identifying genetic and epigenetic elements that influence the immune system. A key goal in this field is to define mechanisms of immune system deviation and immune tolerance and apply this knowledge to generate improvements in asthma care and allergen immunotherapy. A related goal is to further understand the environmental, social, and immunological elements that impact on the development of inner-city asthma through in-depth characterization and longitudinal follow-up of inner-city children from the time of birth. In the past 5 years, NIH budgetary constraints have imposed many challenges for the academic research community. Despite these constraints, NIAID has maintained its support of a highly productive asthma and allergy research program. (*J Allergy Clin Immunol* 2010;125:540-4.)

Key words: *Inner-city asthma, asthma research funding, cockroach allergy*

THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES'S FOCUS ON INNER-CITY ASTHMA

In 1991, the National Institute of Allergy and Infectious Diseases (NIAID) launched its first initiative in inner-city asthma in response to epidemiologic studies that had described the seriousness of asthma as a public health problem in poor, urban communities in terms of prevalence, morbidity, and mortality.¹⁻³

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Abbreviations used

ARRA: American Recovery and Reinvestment Act

FY: Fiscal year

ICAC: Inner City Asthma Consortium

NHLBI: National Heart, Lung, and Blood Institute

NIAID: National Institute of Allergy and Infectious Diseases

NIH: National Institutes of Health

URECA: Urban Environment and Childhood Asthma

Since then, the NIAID has funded 4 consecutive initiatives focusing on inner-city asthma, including most recently a second Inner City Asthma Consortium (ICAC) in fiscal year (FY) 2009. NIAID support has ranged from \$18.7 million for the first of these initiatives to ~\$70 million for the 5 years of the ongoing program. As the article by Busse⁴ in this issue of the Journal describes in detail, the NIAID-funded inner-city asthma studies have significantly increased our understanding of key risk factors for asthma morbidity and have provided the opportunity to evaluate a wide range of interventions, including educational, behavioral, and environmental.^{5,6} Most recently, interventional studies involving guideline-based asthma management⁷ and anti-IgE were completed, all of which have proven to be efficacious.

Asthma remains a serious problem in US inner cities. For example, the most recent figures available through the Centers for Disease Control and Prevention show that, from 2004 to 2005, the asthma mortality rate in black children was 7-fold higher than that of white children, and that this difference had increased between 1999 and 2004.⁸ In a 4-state sample of the 2003 to 2004 Centers for Disease Control and Prevention-funded, National Asthma Survey, Crocker et al⁹ reported that black and Hispanic children, 32% and 22% of whom had a yearly family income <\$15,000, respectively, had more indicators of poorly controlled asthma than did white children, only 6% of whom lived in poverty. Regardless of race or ethnicity, 85% of children included in this sample lived in metropolitan areas. Although the causes that underlie these disparities in asthma morbidity and mortality are not fully known, several factors have been implicated in the NIAID-sponsored inner-city studies, including exposure to high levels of indoor allergens,¹⁰ exposure to high levels of indoor and outdoor pollutants,¹¹⁻¹³ and lack of comprehensive, high-quality medical care.^{14,15} The early NIAID-sponsored observational studies and interventions in inner-city asthma offered particularly strong support for the role of environmental and socioeconomic factors including limited access to high-quality medical care.^{5,10} The last of these factors was explored in depth more recently in the Asthma Control Evaluation study,⁷ which is summarized in the article by Szeffler et al¹⁶ in this issue of the Journal. The Asthma Control

Evaluation study strongly substantiated certain findings and suggestions of earlier NIAID-sponsored inner-city asthma studies, namely, that when provided with consistent and appropriate care, inner-city families are highly motivated to comply with medical regimens and asthma action plans, and young children and adolescents show excellent responses to guideline-based asthma treatment. Furthermore, inner-city families of children with asthma have participated enthusiastically in NIAID-funded studies: subject recruitment met ambitious predefined timelines in the majority of studies; protocol visits were completed at rates exceeding 90% most of the time; families were eager to allow home visits for monitoring and measurement of allergen burdens; and long-term retention in studies has been remarkable, despite the many socioeconomic factors that might predict otherwise. This attests to the overwhelming need of inner-city populations for high-quality care and their eagerness to receive that care. Unfortunately, many of the disparities that spurred NIAID's initial commitment to inner-city patients with asthma persist today, and the structural changes in health care delivery and quality required for resolving this problem have yet to be widely implemented.

The importance of asthma in the inner city has guided NIAID's initial decision and the continuing commitment to focus its asthma research efforts in this environment. Furthermore, the identification of cockroach¹⁰ and mouse¹⁷ allergens as pervasive major environmental allergens of the inner city provides investigators with specific targets for studying asthma overall and for developing new therapeutic approaches to this condition. Another factor strongly associated with asthma, albeit in ways not currently known, is obesity. With obesity increasingly prominent in the inner city, especially in children, there is continued need for comprehensive asthma research in this environment. Indeed, NIAID's ICAC is focusing on obesity and its relationship to asthma in children, as highlighted in the article by Kattan et al¹⁸ in this issue of the Journal. Admittedly, we are still at an early stage of the effort to understand the asthma-obesity relationship, its impact on morbidity, and the best approaches for intervention.

Over the past 2 decades, many studies have pointed to the importance of socioeconomic factors and unique features of the inner-city environment as related to asthma. What particularly distinguishes the NIAID-sponsored efforts is the long-term commitment of ample resources to this area of research; a commitment to working within census tracts where a high percentage of families live below the federal poverty level; a consistent focus on subjects with moderate to severe asthma, as defined by widely accepted criteria; and rigorous study designs that evaluate new approaches in the context of guidelines-based standard of care. Furthermore, the financial and other resources provided by NIAID have enabled relatively large-scale studies of 400 to 600 subjects representative of diverse racial and ethnic groups and the participation of 6 to 10 clinical sites in each study representing a range of geographic, climatologic, and housing parameters that ensure that study outcomes will be broadly relevant.

Since the inception of the inner-city asthma program, NIAID has provided services that are key to the program's success. This includes clinical research organization support, which assists the investigators in study design, protocol preparation and review, preparation of case report forms and manuals of operation, data handling and statistical analysis, clinical site training, and data and safety monitoring. Furthermore, an independent Data and

Safety Monitoring Board reviews all funded clinical trials and reports directly to NIAID. In addition, in all clinical trials that the inner-city asthma program conducts, NIAID's extramural regulatory staff prepares, submits, and holds Investigational New Drug applications. These services ensure high standards in the organization of clinical studies and trials, ensure adherence to clinical research principles and regulations, and allow clinical investigators to focus on the scientific and clinical aspects of study design and execution.

FUNDING ASTHMA RESEARCH UNDER CURRENT ECONOMIC CONSTRAINTS

The National Institutes of Health (NIH) budget doubled from \$13.7 billion in FY 1998 to \$27.1 billion in FY 2003. Over the same interval, the NIAID budget increased from \$1.35 billion to \$3.7 billion, including \$1.16 billion appropriated in FY 2003 to support biodefenses research. This major expansion of budget enabled the Institute to substantially increase funding of clinical research in immune-mediated diseases including asthma and allergic diseases.

Between FY 2005 and FY 2009, the NIH base appropriation has been relatively constant. The FY 2010 NIH appropriation of \$31 billion represents an 8.8% increase over FY 2005 and a 2.3% increase over the FY 2009 budget. These budgetary increases have not kept pace with the annual rate of inflation for research and development as reflected in the Biomedical Research and Development Price Index, which has averaged 4.1% from FY 2005 to FY 2009.¹⁹ As a result, NIH buying power has been reduced by approximately 15% since FY 2005. The American Recovery and Reinvestment Act (ARRA) provided NIH an additional \$10 billion that must be obligated in FY 2009 and FY 2010. Currently, there are no provisos that this 1-time increase in the NIH budget will add to the base appropriation in FY 2011 and beyond. The ARRA funding has been highly beneficial because it has allowed many investigators to continue their research endeavors without disruption, but this boon could contribute to a peer-review and budgetary bottleneck in FY 2011 and FY 2012, when the large number of 2-year awards supported by these funds will expire and competitive renewal applications will be submitted for funding.

Since FY 2005, the NIAID has implemented numerous measures to maintain critical levels of research support, especially of investigator-initiated research grants.²⁰ These measures have included restrictions on yearly inflationary increases in noncompeting awards, a 20% cap on budgetary increases of competing renewal applications, and elimination or substantial reductions in the funding of solicited research programs. So far, NIAID has maintained relatively stable funding for research project grants, the majority of which are investigator-initiated studies.²¹

In response to the current budgetary constraints, the NIAID has substantially reduced funding of many solicited research programs to support paylines and success rates for investigator-initiated research project grants, including those of new and early-stage investigators. In the fields of asthma and allergic diseases, a significant proportion of NIAID funds are committed to solicited research programs, such as the ICAC and the Asthma and Allergic Diseases Cooperative Research Centers. This reflects the priority the Institute places on maintaining a cadre of experienced investigators and trainees and the infrastructure needed to conduct high-quality asthma clinical research in inner-city environments.

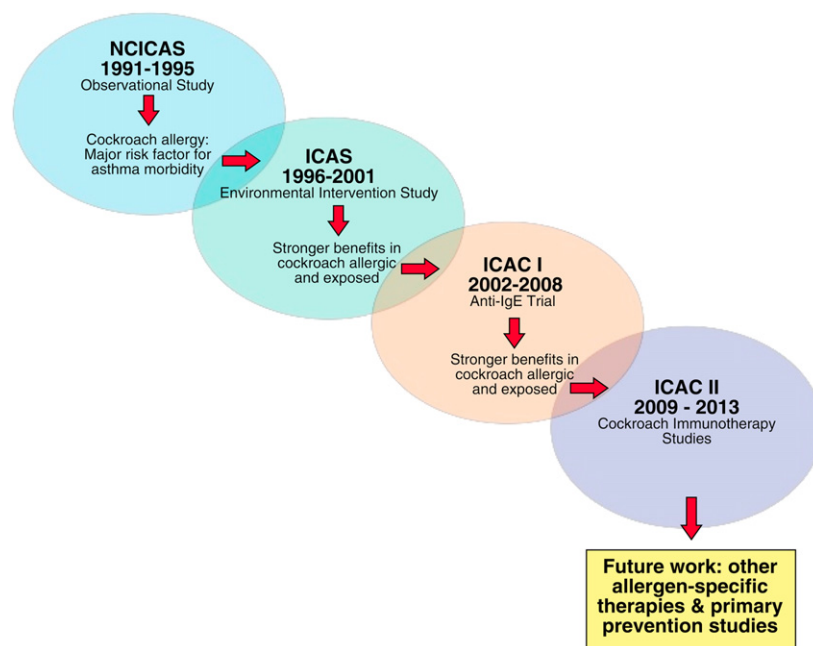


FIG 1. The concept that cockroach allergy plays an important role in inner-city asthma as developed by studies conducted under the NIAID-funded inner-city asthma initiatives over the previous 20 years. ICAS, Inner-City Asthma Study; NCICAS, National Childhood Inner-City Asthma Study

Moreover, these NIAID priorities reflect the Institute's commitment to address a significant and longstanding health disparity with implications for the well being of millions of Americans. Therefore, despite the aforementioned financial constraints, the NIAID has made substantial efforts to maintain support for clinical research programs in asthma and allergic diseases as well as a scientifically robust investigator-initiated research program. As a result, NIAID expenditures for solicited research in asthma and allergic diseases increased from \$53.6 million in FY 2005 to \$60.2 million* in FY 2009, including \$8.5 million of ARRA expenditures. Investigator-initiated awards in the fields of asthma and allergic diseases were supported by \$53.8 million in FY 2005 and \$67.6 million in FY 2009, including \$15.3 million from ARRA. The NIAID will endeavor to maintain the total number of investigator-initiated awards during the upcoming fiscal years by identifying opportunities for synergy and greater efficiencies, and by pursuing program priorities developed in consultation with the research community.

PRIORITIES IN INNER-CITY ASTHMA RESEARCH AND ONGOING ASTHMA AND ALLERGY RESEARCH PROGRAMS

As discussed by Busse⁴ in this issue of the Journal, the original NIAID-funded inner-city asthma initiatives focused on identifying risk factors for asthma morbidity and conducted comprehensive interventions targeting environmental asthma triggers. Although those interventions proved efficacious in reducing asthma disease activity, it became evident that the feasibility of implementing them at a large scale, in the context of a nationwide

public health initiative, would be low. Yet these interventions provided the proof-of-concept that high allergen exposure of sensitized individuals played a significant role in asthma morbidity and led to a new focus for subsequent NIAID inner-city asthma initiatives, asthma immunopathology, and immunotherapeutics. Thus, the current goal of the ICAC is to understand further the immune mechanisms that are operative in inner-city asthma and to use immunomodulatory approaches for treatment and prevention. Of particular interest is the allergic component of the disease and the possibility of developing new forms of allergen immunotherapy that will render this method of treatment more efficacious, rapid, long-lasting, safer, and cost-effective. The long-term goal is to minimize asthma morbidity and the prevalence of asthma by using preventive interventions.

A key objective of the NIAID inner-city asthma program is to augment the clinical trials of ICAC with tightly-associated mechanistic research. In this spirit, ICAC has incorporated 2 basic science sites to collaborate closely with its 8 clinical sites. Also, the NIAID expects that its inner-city asthma studies will range from exploratory, hypothesis-generating to hypothesis-testing so that research on a specific topic can proceed from initial observation to clinical applicability. To accomplish this, the NIAID inner-city asthma programs have involved comprehensive and multifaceted approaches using observational and interventional studies. The identification of cockroach allergy as an important factor in inner-city asthma morbidity exemplifies this approach (Fig 1). The first inner-city asthma observational study conducted by the National Childhood Inner-City Asthma Study team was pivotal in raising awareness that cockroach sensitization and exposure is a risk factor for asthma severity in this environment¹⁰ and generating testable hypotheses regarding environmental remediation and, eventually, cockroach allergen immunotherapy. The first of these hypotheses was substantiated by the comprehensive environmental intervention conducted by

*Reflects FY 2009 prorated portion (\$12.2 million) of \$61.2 million awarded under NO1A1900052 in FY 2009 to fund ICAC activities fully from FY 2009 to 2013.

the Inner-City Asthma Study.⁵ Further support has been recently generated by the Inner-City Anti-IgE Therapy for Asthma study, the data from which indicated that those who benefit most from this therapy have allergic sensitivity and high exposure to cockroach. The program has moved on to its next step, testing of cockroach-specific immunotherapy for asthma. This newest research effort is likely to involve studies that span all phases of drug development and may proceed beyond conventional allergen immunotherapy to include adjuvants or epitope-specific therapeutic materials. This satisfies another objective for NIAID wherein, through a program that targets a specific allergen of well established clinical importance, new therapeutic strategies can develop that may have applications in other areas of allergy and immunology.

A major addition to the NIAID's inner-city asthma program was the implementation of the Urban Environment and Childhood Asthma (URECA) study, a birth cohort study initiated in 2004 to identify early factors influencing the development of asthma in inner-city populations. Details on URECA are presented in the article by Gern²² in this issue of the Journal. URECA, unlike other asthma birth cohorts, places major emphasis on the development of the immune system primarily in relationship to environmental factors. In this respect, we expect that the information obtained from this study will be valuable not only in the context of inner-city asthma but also as a resource to the NIAID's broader interests in neonatal and pediatric immunity and in the human immune system profiling program. This program, to be initiated in FY 2010, will create a network of research centers that will profile human immune responses before and after an immune challenge, including natural infections and vaccinations against infectious diseases. The objective is to examine the diversity of human immune responses under a variety of conditions using bioinformatic, multiplex, and/or systems biology approaches.

In addition to the ICAC, which is a central element in NIAID's asthma and allergy scientific program, the Institute supports 15 Asthma and Allergic Diseases Cooperative Research Centers across the United States. These centers conduct clinical and basic research including studies to understand the function of various cells in airway inflammation and the allergic process, studies exploring how airway infections and environmental pollution interact with allergy, genetic studies in asthma and allergy, and clinical trials and mechanistic research in food allergy. Furthermore, NIAID research in asthma and allergy is supported by studies conducted by several other sponsored initiatives: the Immune Tolerance Network has focused its allergy program on early prevention of peanut allergy and ragweed allergen immunotherapy^{23,24}; the Consortium in Food Allergy Research conducts observational work and clinical trials of food allergy immunotherapy; the Atopic Dermatitis and Vaccinia Network, currently under recompetition as the Atopic Dermatitis Research Network, examines atopy-related immune dysfunction in cutaneous tissues and its impact on innate and acquired immunity; and finally, the centers supported by the Allergen and T-cell Reagent Resources contract are working to identify and map T-cell epitopes of major allergens for future use in immunodiagnostics and immunotherapy. Added to these programs is the large portfolio of investigator-initiated research projects, which span all aspects of basic and applied immunology.

Overall, the current scientific focus of the NIAID in asthma and allergy includes mechanisms of immune system deviation and how they can be applied in immunophenotyping patients; mechanisms of immune tolerance and how they can be applied in

immunotherapy; the interaction of the immune system with infectious agents, including viruses and other microbes; the identification of biomarkers to be used in prospective cohorts and clinical trials; and the identification of genetic and epigenetic elements influencing the immune system. In the context of these research areas, the interaction of the indoor and outdoor environment with the immune system is especially pertinent given the adjuvant role played by many environmental stimuli and pollutants.

TRANS-AGENCY AND PUBLIC-PRIVATE PARTNERSHIPS IN ASTHMA RESEARCH

In addition to the NIAID and the National Heart, Lung, and Blood Institute (NHLBI), other NIH institutes, as well as other government agencies and nongovernmental organizations, have longstanding interests in asthma research and are increasingly supporting projects in the field. NIAID recognizes the need and the importance for trans-agency and public-private partnerships and has taken the lead or participated in activities to promote such collaborations. For example, in the 1990s, the National Institute of Environmental Health Sciences (NIEHS) cofunded NIAID's second inner-city asthma initiative, and the Environmental Protection Agency provided support for rigorous monitoring of indoor and ambient air quality. In FY 2004, the NIAID and the NHLBI cofunded the Immune System Development and the Genesis of Asthma initiative and in FY 2005 the Asthma Exacerbations: Biology and Disease Progression initiative.

Two recent collaborations are important to mention. In FY 2009, the NIAID partnered with the NHLBI and its Severe Asthma Research Program centers to conduct a clinical trial evaluating the efficacy of an H1N1 influenza vaccine in individuals with severe (receiving high doses of inhaled steroids and/or oral steroids) and mild/moderate asthma. This study was needed because the 2009 H1N1 influenza epidemic was disproportionately severe in people with asthma (asthma was an underlying condition in close to 30% of patients hospitalized with H1N1 influenza²⁵). This very successful collaboration allowed 390 subjects to be enrolled and vaccinated in less than 5 weeks.

Recognizing the need for harmonization of asthma clinical trials with respect to outcome measures, the NIAID has recently partnered with the NHLBI, the National Institute of Environmental Health Sciences, the National Institute of Child Health and Human Development, the Agency for Healthcare Research and Quality, the Merck Childhood Asthma Network, and the Robert Wood Johnson Foundation to host the Asthma Outcomes Workshop in March 2010. The objective of this workshop is to develop standardized definitions and data collection methodologies for established and validated outcomes measures, with the ultimate goal that these outcomes will be broadly used in the future in all NIH-funded asthma clinical trials and epidemiologic or cross-sectional studies.

ASTHMA AND ALLERGY: HELPING UNDERSTAND THE ENTIRE IMMUNE SYSTEM

The study of asthma and allergic diseases provides information that has implications beyond these nosologic entities, into areas of autoimmunity and transplantation, where the immune system plays an equally important role. One advantage of using allergy as an experimental model is that, in most cases, the offending antigen is known, and exposure to this antigen is not constant.

This allows observations to be made when the immune system is naturally (eg, seasonally) stimulated and when it is in a relatively quiescent phase. Furthermore, because some of the local allergic reactions in the skin or even in the respiratory or the gastrointestinal tract can be experimentally induced with relatively low risk, research in allergy can unravel details of immune responses that would be hard to obtain in other immune-mediated disorders. Finally, the development of allergic sensitization and the eventual natural resolution that occurs during the transition from childhood to late adolescence (eg, egg and milk allergy, atopic dermatitis) can be studied in longitudinal cohorts and can be compared with experimentally induced desensitization or tolerance that can be achieved through allergen immunotherapy. These types of studies can offer invaluable information on the immune profiles that serve as signatures of immune sensitization and on the induction and maintenance of immune tolerance. The NIAID has major programmatic interests in this area of research and expects to maintain a strong commitment to funding this research in the future.

The NIAID inner-city asthma research program has spanned 2 decades of high productivity and has provided important information that can directly benefit people with asthma who live in resource-poor, urban environments. In addition, the scientific community is benefitting from the generalization of these findings in the entire asthma and allergy field and in the broader field of immunology. Although NIAID has provided the resources for the inner-city asthma research programs and is proud of these achievements, they are the direct result of the ingenuity and commitment of the many scientists and research staff that have conducted this work. Most importantly, these successes were achieved thanks to the thousands of inner-city families who have enthusiastically participated in these studies.

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