

Incentive to study drugs in children and other governmental initiatives: Will patients with asthma benefit?

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This article summarizes current regulations that have been developed to facilitate the performance of pediatric drug trials and their impact on children, particularly those children affected with asthma. In addition, other initiatives that have been developed by the federal government in response to the unexplained increase of asthma occurrence during the last 15 years will be reviewed. In the face of an asthma epidemic, a comprehensive approach is needed to determine the causes for the increase in the prevalence rate and the role of aeroallergens and other environmental and genetic factors and to identify effective preventive measures. Clearly, facilitating drug trials to prove the safety and effectiveness of drugs is of paramount importance. (*J Allergy Clin Immunol* 2000;106:S118-24.)

Key words: Pediatric drug trials, pediatric labeling, Pediatric Pharmacology Research Unit Network, Pediatric Rule of 1998, biomarkers

With the exception of antibiotics used to treat common infections, most drugs that are administered to children are not labeled for pediatric use. This lack of testing of drugs in children is a situation that has been recognized for over 3 decades.¹

The Food and Drug Administration (FDA) regulatory position was clearly articulated in 1970 when the agency declared that drugs used in children must be tested in children.² Over the next 20 years, no significant progress was made. The percentage of drugs that were used in children but not labeled for pediatric use was 78% in 1973 and 81% in 1992.^{3,4}

FINDING A SOLUTION

In 1997, Congress passed the Food and Drug Administration Modernization Act (FDAMA).⁵ Section 111 of this Act provides a financial incentive to pharmaceutical companies that conduct pediatric drug trials that leads to labeling.

The seminal work that eventually led to the passage of this incentive can be traced to a Workshop of the Forum on Drug Development of the Institute of Medicine of the

Abbreviations used

DHHS:	Department of Health and Human Services
FDA:	Food and Drug Administration
FDAMA:	FDA Modernization Act
NHLBI:	National Heart, Lung, and Blood Institute
NIAID:	National Institute of Allergy and Infectious Diseases
NICHD:	National Institute of Child Health and Human Development
NIH:	National Institutes of Health
PPRU:	Pediatric Pharmacology Research Unit

National Academy of Sciences in 1990. The Workshop was convened to address the issue of the lack of pediatric drug labeling. Invited participants included members of the American Academy of Pediatrics and representatives from pharmaceutical companies, academia, and the National Institute of Child Health and Human Development (NICHD). Several recommendations emanated from this Workshop, a number of which were adopted over the ensuing years. It was recommended that the FDA facilitate pediatric drug labeling by allowing the use of published information and the extrapolation from adults to children as evidence of efficacy.

The FDA followed these recommendations by incorporating them in the Pediatric Final Rule of 1994. This rule applied to approved drugs and biologics and stated that "a pediatric indication may, in some cases, be based on adequate and well-controlled studies in adults, with other information supporting pediatric use" (59 Federal Register 64240). Pediatric drug labeling submission under this rule was voluntary.

The response to the Pediatric Rule of 1994 was disappointing and did not produce the expected favorable response from pharmaceutical companies. Although there were 430 submissions for labeling changes, only 15% of the applications contained adequate data for drug labeling at all ages. No improvements in drug labeling resulted from 330 applications. Nevertheless, the Pediatric Rule of 1994 is still in effect as a vehicle for pediatric drug labeling changes.

A major concern at the time of the Workshop was the feasibility of the performance of drug-labeling studies in children of all ages, especially infants. To address these concerns, the Workshop participants recommended that the NICHD provide the infrastructure for a multicenter network. In response to this recommendation, the NICHD created the Pediatric Pharmacology Research Unit Network in 1994. The Network originally com-

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prised 7 units (PPRUs), all with programs in pediatric pharmacology already in place. All PPRUs have a pharmacology laboratory, which uses highly sensitive quantitative methods to measure drugs and their metabolites with the use of small amounts of blood. The PPRU scientists developed or adapted pharmacokinetic techniques applicable to children of all ages.

The network was successful in proving that, with appropriate expertise and technical support, drug studies can be safely and ethically performed in children, regardless of age and disease state. The network completed studies leading to labeling for a variety of drug classes and pediatric age groups.

These efforts were recognized by the US Congress Committee of Conference of the House and Senate (Bill S8301: FDAMA) that noted "the excellent efforts of the National Institutes of Health, especially through the Pediatric Pharmacology Network which will contribute significantly to this effort." Also, in the Preamble to the Final Pediatric Rule of 1998, the FDA stated that, "the PPRU Network has an established record of recruiting pediatric patients and completing valid studies."

CURRENT REGULATORY INITIATIVES

The pediatric provisions of FDAMA and the Pediatric Rule of 1998⁶ are the 2 legislative and regulatory initiatives that will profoundly affect pediatric drug development well into the 21st century. The FDAMA provides a 6-month extension of exclusivity for marketed drugs with unexpired patents or for drugs that have been granted other kinds of exclusivity. This strong economic incentive represents a powerful engine to drive new research initiatives.

In contrast to the voluntary nature of FDAMA, the Pediatric Final Rule of 1998 that became effective on April 1999 is a compulsive regulation. The final Pediatric Rule of 1998 is mostly applicable to new molecular entities with indications in pediatrics, although some marketed drugs may be included if the FDA concludes that pediatric studies are needed. These 2 regulatory and legislative initiatives have been designed to complement each other. There are limitations in the scope and effect of the exclusivity offered in FDAMA that can lead to significant gaps in pediatric drug labeling. For example, most off-patent drugs, most antibiotics, and older drug products with no remaining exclusivity are not covered under FDAMA. Also, the voluntary nature of FDAMA will result in many drugs remaining unlabeled (eg, market forces may limit studies in certain age groups for certain drugs). In addition, pharmaceutical companies may be granted exclusivity if they follow the terms of the FDA written requests (*vide infra*), regardless of whether the studies lead to a label change.

The time course of the 2 regulations is different. The incentives created by FDAMA became effective on November 21, 1997, but the provisions sunset on January 1, 2002. In contrast, the studies mandated by the Pediatric Final Rule of 1998 are not required until December 2, 2000, but after implementation there is no sunset date.

PEDIATRIC PROVISIONS OF FDAMA

The economic incentive in the form of 6 months of additional marketing exclusivity is the key provision of this legislation. Section 111 of FDAMA requires the Secretary of the Department of Health and Human Services (DHHS), "after consultation with experts in pediatric research, to develop, prioritize, and publish a list of approved drugs for which additional information may produce health benefits in the pediatric population," and that, "the Secretary shall annually update the list." To compile the list, the FDA consulted with various organizations that included the Committee on Drugs of the American Academy of Pediatrics, the Pediatric Pharmacology Research Unit Network, the US Pharmacopeia, the Pharmaceutical and Manufacturers of America, sponsors, and FDA staff. The first list was published in the Federal Register on May 20, 1998,⁷ and contained 480 drugs. A second revised list was published a year later. The drugs in those lists are grouped according to the review divisions of the Center for Drug Evaluation and Research of the FDA. Fig 1 shows the frequency distribution of drugs in the list according to the review divisions. The cardiorenal division was assigned the largest number of drugs because of the large number of antihypertensive medications on the market. The drugs for the treatment of asthma included in the 1999 list, and the age groups for which studies are needed are listed in Table I.

To implement FDAMA, the FDA developed a process under which pharmaceutical companies propose to the agency pediatric studies of drugs that are included in the list. If the requests are approved, the FDA issues a written request to the sponsors that details the type of study to be performed. If the sponsor performs the studies according to the agency specifications, a 6-month market exclusivity is granted regardless of whether the resulting data lead to a change in label.

As of August 1, 1999, 143 proposed pediatric study requests were received in the agency. Nine of those proposed pediatric studies filed by pharmaceutical companies were antiasthmatic drug requests, with leukotriene modifiers among the accepted requests. At the time of the implementation of FDAMA, the FDA expected that most proposals would require dosing and safety studies. The initial expectation was based on the requirements of the FDA Pediatric Rule of 1994, which allows the extrapolation of adult efficacy studies if the history of a disease, its pathophysiology and response to therapy is similar in children and adults. Unexpectedly, an analysis of the written proposals that was conducted by the Center for Drug Evaluation and Research divisions revealed a large percentage of the proposals would require efficacy studies. The agency concluded that there might be significant dissimilarities in disease expression or response to therapy between children and adults with certain disorders such as hypertension, depression, and asthma. In such cases, depending on the drug and the specific labeling changes requested, efficacy studies would be required. Therefore, the FDA still evaluates whether any proposal for pediatric use would need to include additional efficacy studies.

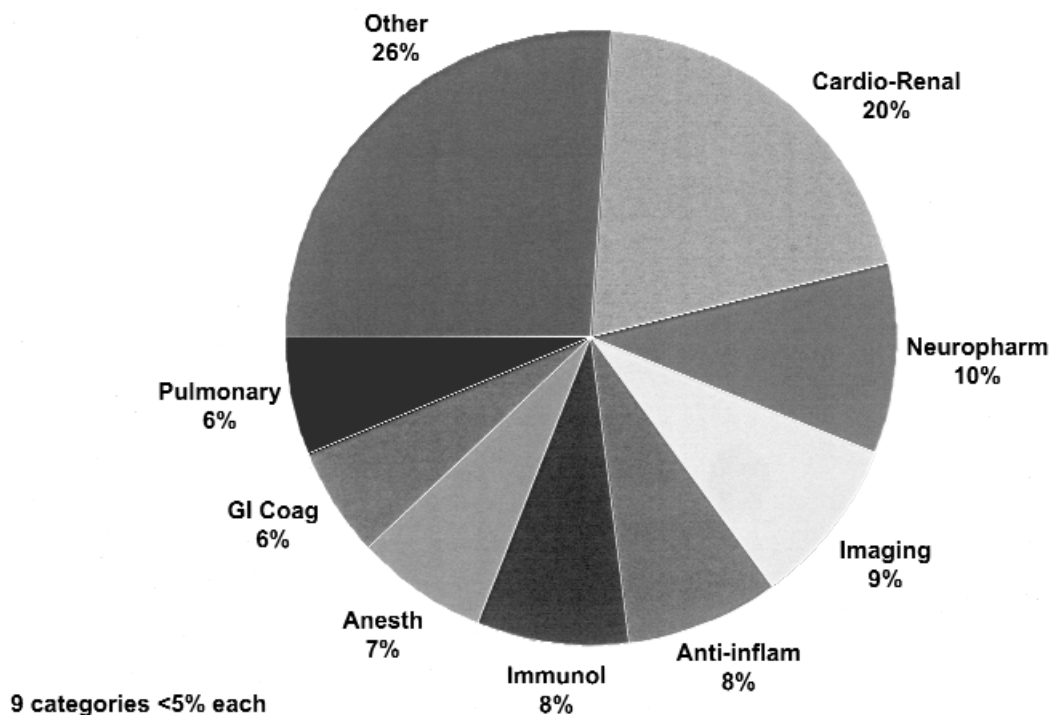


FIG 1. Frequency distribution of drugs in the FDA list, according to FDA review divisions. *GI Coag*, Gastrointestinal coagulation.

TABLE I. Asthma drugs in the 1999 FDA list

Drug	Age groups needed (y)
Bitolterol	All ages
Budesonide	<6
Fluticasone	<4
Flunisolide	?
Metaproterenol	<6
Montelukast	<6
Nedocromil	<6
Pirbuterol	All ages
Salmeterol	All ages
Terbutaline	All ages
Triamcinolone	<6
Zafirlukast	<12
Zileuton	<12

FINAL PEDIATRIC RULE OF 1998

The subject of this rule includes new chemical entities, new indications, new dosage requirements, new dosage forms, and new routes of administration. Pediatric studies will be required for new drugs if the drug or biologic offers a meaningful therapeutic benefit and if the absence of labeling poses a risk to pediatric patients or if there is an anticipated use in a substantial number of pediatric patients.

The rule defines a "meaningful therapeutic benefit" when a drug offers a "significant improvement in the treatment, diagnosis or prevention of a disease compared with marketed products adequately labeled for that use in the relevant pediatric population or the drug is in a class of

drugs or for an indication for which there is a need for additional therapeutic options" (63 Federal Register 6631-66672. Available at: <http://www.fda.gov/ohrms/dockets/98fr/120298c.txt>). The rule defines "substantial use" as annual use in more than 50,000 patients.

The Pediatric Rule of 1998 includes all pediatric age groups (including newborns) and mandates the development of pediatric formulations when needed. The FDA may grant waivers or deferrals.

Grounds for waivers are (1) the criteria for "meaningful therapeutic benefit" and "substantial use" are not met, (2) the product is unsafe or ineffective in pediatrics, and (3) reasonable efforts to develop a needed formulation have failed. The criteria for deferrals are (1) a new drug for adult use is ready for approval before pediatric studies are completed and (2) additional safety or effectiveness information is needed in adults.

The rule stipulates that the "FDA will convene a panel of experts, including at least one industry representative, and seek its advice on a range of issues related to the implementation of the rule" (63 Federal Register 6631-66672. Available at: <http://www.fda.gov/ohrms/dockets/98fr/120298c.txt>). The activities of the Pediatric Advisory Subcommittee are to provide an annual oversight of the implementation of the rule, including waivers and deferrals; to discuss ethical issues raised by clinical trials in pediatric patients; to review trial design and data analysis; to review the need for additional therapeutic options; to recommend specific marketed drugs and biologic products that should be studied in pediatric patients; and to provide oversight on the progress of studies.

PROBLEMS WITH THE NEW REGULATIONS AND IMPLICATIONS FOR THE FUTURE

The major problem in the implementation of the new regulations is that there is no systematic process to establish criteria for the identification and prioritization of the most important drugs for pediatric use and to compare similar diseases or conditions that affect children and adults.

To a great extent, the implementation of FDAMA is driven by market forces. It can be argued that testing in children of different types of antihypertensives for essential hypertension should be delayed until indications for treatment in children are better defined. "White coat" hypertension remains an important issue, and there is a lack of standardization in outpatient monitoring of blood pressure in children. More fundamentally, the issue of efficacy remains unresolved. Large adult trials of thousands of patients that used coronary artery disease and incidence of stroke as clinical endpoints were needed to validate blood pressure measurement as a surrogate endpoint. The long interval between the detection of high blood pressure in children and the occurrence of either coronary artery disease or stroke precludes the use of these clinical endpoints in this population.

Although several studies on antihypertensive drugs are being conducted, the dosing effectiveness and safety of drugs used for antiarrhythmics, anticoagulants, thrombolytic agents, and vasopressors remain unexplored in children. Because of the lack of evidence of efficacy, each patient becomes an experiment, and doses are often educated guesses. Newborns represent a subpopulation within pediatrics in which drugs are more often used empirically without proof of efficacy. Even with the implementation of the Pediatric Rule of 1998, it is unlikely that the hundreds of drugs currently in use in newborns will be studied. Therefore, a prioritization system based on the frequency of use, therapeutic index, and use in life-threatening or chronic conditions must be developed to select drugs that need to be studied.

The explosion of studies initiated or proposed as a consequence of FDAMA has also revealed the need to expand the current knowledge of pediatric drug trial methods and developmental pharmacologic capabilities.

Research on clinical trial methods must include the evaluation of biologic responses. The study of biomarkers as indicators of pathogenic processes of disease may yield important information on the natural history of pediatric diseases and their response to therapeutic intervention. Biomarkers could also permit stratification according to disease severity and selection of a homogeneous population. Proof of efficacy in severe asthma is often elusive because of the heterogeneity of the population studied. Severe asthma has been linked recently to low concentrations of tracheal S-nitrosothiols.⁸ Validation of this or other biomarkers could allow a reduction in the number of children needed to demonstrate efficacy of antiasthma medications. Longitudinal studies of biomarkers in chronic disease, such as asthma, would not only allow the monitoring of the progression and recur-

rence of the disease but would also permit the use of these measurements as intermediate surrogate endpoints.

Because the beginnings of pediatric asthma are traced to a much younger age, the development and validation of clinical endpoints in infants becomes of paramount importance.

The major challenge ahead will be to close the gap in the current understanding of the ontogeny of drug-metabolizing enzymes, transporters, and receptors. The change in the pharmacologic paradigm from symptomatic relief to targeting the cause or mediators of the disease underscores the need to acquire this new knowledge. The development of leukotriene modifiers, the first major therapeutic advance in the treatment of asthma in 10 years, illustrates this point.

The NICHD has recognized the need to advance the field of pediatric trial methods and developmental pharmacologic examination. To this end, the Institute not only increased the number of centers comprising the PPRU Network from 7 to 13 but also increased its scope to include research in these areas.

THE ASTHMA EPIDEMIC

Over the last 15 years, the number of patients with asthma has more than doubled. Data from the National Center for Health Statistics indicated that the number of individuals affected with asthma increased by 7.8 million individuals in the United States between 1980 and 1996.⁹ Based on statistical projections, the Centers for Disease Control and Prevention estimated that in 1998, approximately 17.3 million individuals in the United States were affected with asthma.¹⁰

The increasing prevalence is a worldwide phenomenon that affects both children and adults. A number of studies have documented the increased prevalence of asthma in many countries during the last 2 decades.¹¹⁻¹⁴

The European Community Respiratory Health Survey¹⁵ and the International Study of Asthma and Allergy in Children¹⁶ have provided reliable data on the current prevalence of asthma in different countries. There are large differences in the prevalence of asthma between countries and within geographic regions. New Zealand, the United Kingdom, Australia, and Ireland have high prevalence rates of asthma in children; China has a low prevalence of asthma in children. There are also marked differences within a given country.

The causes for the marked increase in the prevalence of asthma remain elusive, and it is remarkable that the increase occurs during a period of great strides in the understanding of its pathophysiologic features. The greatest increases in the United States occurred in children under 5 years of age; the number of cases increased more than 150% in the last 15 years.¹⁷ Total deaths from asthma have increased significantly since 1977 (1674 deaths in 1977 to 5637 deaths in 1995).¹⁸ Although the number of asthma deaths is relatively low, the percentage increase is most disturbing, considering that the mortality rates in persons with other chronic conditions are decreasing.

ASTHMA IN CHILDREN

Asthma is the most common chronic disease of childhood, with 4.8 million affected children in the United States.¹⁹ It is more common in school children than in preschool children; 1 of every 13 school children is affected. It is a major cause of school absenteeism and is a contributing cause to an estimated 10 million missed school days annually.²⁰

Asthma death rates in children between ages 5 and 14 years almost doubled between 1980 and 1993 (17 and 32 asthma deaths per million population, respectively). From 1993 to 1995, black children were 4 times more likely to die of asthma than white children.¹⁸

Asthma severity is significantly increased in urban minority populations, both black and Hispanic. Children living in inner cities often do not receive appropriate treatment to prevent or reduce the severity of the disease. Eggleston et al²¹ studied asthma treatment received by a group of elementary school children in the less affluent areas of Washington DC and Baltimore, Md. A significant number of the children who were studied were either under medicated or were taking the wrong medication, and more than 80% of the children had not received anti-inflammatory drugs.

FEDERAL GOVERNMENT INITIATIVES TO DEAL WITH THE ASTHMA EPIDEMIC

In response to the staggering increase in the prevalence of asthma, the Secretary of the DHHS, Dr Donna E. Shalala, spearheaded the development of a strategic plan termed *Action Against Asthma*.²² This plan, currently in draft form, establishes 4 priorities over the next 5 years:

1. Determination of the causes of asthma and the development of strategies to prevent the disease
2. Reduction of the burden for people living with asthma
3. Elimination of the disproportionate burden of asthma in minority populations and those living in poverty
4. Tracking of the disease and assessment of the effectiveness of asthma intervention programs

The plan acknowledges the need for a comprehensive approach that includes strengthening of public health and educational programs, control of the environment (indoors and outdoors), improved access to care, and the widespread use of scientific knowledge to prevent or reduce the severity of the disease. In addition, the plan would establish a comprehensive data system to track the disease and assess the effectiveness of asthma programs at the local, state, and national levels.

President Clinton, concerned over the scientific evidence that demonstrated that children in the United States endure a disproportionate burden from environmental health risks, issued an executive order in 1997 that directed federal agencies to identify, assess, and address those risks. To this effect, a task force on environmental health risks and safety risks to children was created. In 1998, the task force identified childhood asthma as 1 of 4 priority areas that require immediate attention.

EXPANSION OF RESEARCH ACTIVITIES

The prohibitive costs of asthma underscore its health costs and the need for further research as to the causes of the current asthma epidemic. In 1990, the cost of asthma in the United States was estimated to be 6.2 billion dollars.²³ Six years later, the cost estimated by a different source was calculated to be 14 billion dollars.²⁴

In fiscal year 1999, the DHHS invested 125 million dollars in research of which the National Institutes of Health (NIH) received the largest share, \$115 million. A substantial increase in research funding is planned for the next fiscal year.

NIH RESEARCH INITIATIVES BENEFITTING CHILDREN WITH ASTHMA

Many NIH research initiatives will directly or indirectly benefit children with asthma. In September 1999, the National Institute of Allergy and Infectious Diseases (NIAID) funded the Allergic Diseases Research Centers, a multidisciplinary research program to perform basic and clinical research on mechanisms, treatment, and prevention of asthma. Research objectives for these centers include:

1. The study of T-cell-mediated immune tolerance for asthma prevention
2. The study of molecular and cellular mechanisms by which viruses cause inflammation in asthma
3. The study of receptors that mediate negative signaling in immune and inflammatory cells
4. Clinical trials of immune modulation therapy

Recent research points to permanent abnormalities in lung function in a substantial number of patients with asthma as a consequence of airway injury and repair. To address this problem, the National Heart, Lung, and Blood Institute (NHLBI) funded studies on airway remodeling and repair in September 1999. The research objectives of this program include the study of the relationship of the pathologic, ultrastructure, and morphometric features of remodeled airways in asthma and the role of airway remodeling in the natural history of the disease. It is also expected that appropriate animal models of airway remodeling will be developed.

Other areas of NHLBI-supported research are studies of the cellular and molecular mechanisms that regulate β -adrenergic receptors. There is evidence that a decrease in β -adrenergic receptor function may contribute to the severity of asthma. There is, however, a dearth of information on the ontogeny of airway β -adrenergic receptors. It is known that repeated exposure to β -agonist drugs may lead to a desensitization of drug response. This process may decrease β -adrenergic responsiveness and thus decrease the effectiveness of β -agonistic bronchodilators. The ontogeny of β -adrenergic desensitization in the rabbit tracheal muscle has been recently studied.²⁵ It was found that the β -adrenergic desensitization mechanisms increase with postnatal maturation. The ontogeny of lung β -adrenergic receptors remains an untapped area of research.

The NHLBI also supports research on the origins of asthma in early life. The role of T_{H1} and T_{H2} responses and of T_{H1}/T_{H2} immune deviation in determining the development of asthma is being currently investigated.²⁶ The unraveling of the factors that modulate the immune response (from a T_{H2} -like response to a mature T_{H1} -like response) may be important for the determination of the causes of asthma and the development of effective preventive strategies. Although the effect of maternal factors in programming the immune response of the fetus and newborn has not been studied in great detail, there is experimental evidence that lends support to the concept of in utero priming.

Immune responses similar to those of allergy sensitization have been reported as early as 8 to 10 weeks of gestation. Epidemiologic associations (eg, cigarette smoking during pregnancy and risk of asthma in the offspring) also provide stimulus for this research.²⁷

The NHLBI funded studies in April 2000 to elucidate the cellular and molecular mechanisms that underlie nocturnal asthma and its relationship with sleep. This initiative also involves the study of the role of circadian rhythms of endogenous catecholamines and steroids in nocturnal asthma. It is not known whether the endogenous mechanisms involved in nocturnal asthma are similar in children and adults.²⁸

The NIAID is funding a multicenter study to determine the natural history of asthma in early childhood and the effect of diverse environmental allergens (cockroaches, house dust mites, mold, and other allergens). Cockroaches produced a stronger antigen than house dust mite. There are important geographic differences in the distribution of environmental allergens. For instance, the inner cities of Baltimore and Boston have a high rate of cockroach infestation; however, in the southwest of the United States, *Alternaria* appears to predominate.²⁹ It remains unclear, however, whether aeroallergens have a causative role in asthma or whether sensitization to specific antigens represents a genetic predisposition to different aeroallergens with geographic distribution that determine the type of antigen involved.

The lower rates of asthma in China have been ascribed to a protective effect of infestation with parasites.³⁰ The immunologic mechanisms of this purported protection remains unknown, although parasitic infection is known to induce a relative T_{H2} response. Low levels of infection appear to increase the prevalence of asthma, and high levels of infection appear to reduce asthma. The role of environmental "protective" factors is a fertile area for future research.

Several NHLBI funding studies are assessing the effectiveness of reducing exposure to known allergens. The exposure of children who reside in low-income urban areas is being investigated because allergen exposure in this group is associated with disproportionate rates of severe asthma.

The NHLBI and NIAID participate in a genome-wide search to identify genes that may be responsible for susceptibility to asthma. The National Institute of Environ-

mental Health Sciences is also expanding its research program on genetic susceptibility to environmentally related diseases such as asthma. Clearly, gene research and environmental interactions with those determinants may be quite complex.³¹ Among the research being funded is an epidemiologic study in children who live in southern California. This study evaluates the relationship between asthma and exposure to ozone, acid aerosols, and nitrogen oxides. The research will also examine genes that may be responsible for the susceptibility of the airway to the effects of ozone.

The NHLBI supports several large pharmacotherapy research programs in asthma. The Childhood Asthma Management Program is the largest outcome study of asthma ever undertaken. The purpose of the program is to compare the long-term effects on lung growth and the safety of 3 treatment strategies for asthma in children aged 5 to 12 years at enrollment. Inhaled budesonide and nedocromil are compared with a placebo group. A 5- to 6-year follow-up is planned. From December 1993 through September 1995, 1041 children were enrolled.

In September 1999, the NHLBI funded a Pediatric Asthma Clinical Network. Funding is used to provide the infrastructure for 6 centers and a coordinating center. The purpose of the network is to evaluate novel therapies and management strategies used for pediatric asthma.

The NICHD PPRU network evaluates new chemical entities and drugs that are frequently used in the pharmacotherapy of asthma. This network performs phase II pharmacokinetics and pharmacodynamics trials that involve infants and young children and conducts drug metabolism studies. It is anticipated that the NICHD and the NHLBI networks will interact and complement each other.

Besides the NIH, other governmental agencies are involved in an array of activities that range from promoting the effectiveness of NHLBI guidelines for the diagnosis and treatment of asthma to ensuring access to care and improving surveillance and health services delivery.

The Agency for Health Care Policy and Research funds a number of initiatives in pediatric asthma. One study examines the relationship between a general multidimensional approach and a disease-specific approach. The Agency for Health Care Policy and Research is also funding a large 5-year randomized clinical trial that will test the cost-effectiveness of the recently developed guidelines that were developed to decrease asthma morbidity in children. This study will be completed in the year 2001.

CONCLUSIONS

The enactment of legislation that provides incentives for the testing of drugs in pediatrics constitutes a major step toward the goal of ensuring that children receive drugs that are safe and effective. Critical breakthroughs in pharmaceutical research have resulted in the develop-

ment of new drugs, such as leukotriene modifiers, that modify pathophysiologic processes associated with asthma rather than providing symptomatic relief.

Clearly, facilitating pediatric drug trials to prove the safety and effectiveness of drugs is of paramount importance. In the face of an asthma epidemic, however, a comprehensive approach is needed to determine the causes for the increase in the prevalence rate, the role of aeroallergens, and other environmental and genetic factors and to identify effective preventive measures. In this regard, governmental incentives are important to stimulate basic research, to develop adequate public health interventions for children at risk, and to assess the effectiveness of asthma programs.

The unraveling of the complex interplay of factors responsible for the development of asthma at the cellular and molecular levels will eventually lead to new drugs and interventions that will target the causes of the asthma phenotype. There is also a need to coordinate governmental initiatives with the activities sponsored by universities, the pharmaceutical industry, and private and community-based organizations. The current asthma epidemic can only be curbed and eliminated with a comprehensive and holistic approach.

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