GROWING UP HEALTHY

AN OVERVIEW OF THE NATIONAL CHILDREN'S STUDY

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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U.S. ENVIRONMENTAL PROTECTION AGENCY

THE NATIONAL CHILDREN'S STUDY

HEALTH GROWTH ENVIRONMENT

GROWING UP HEALTHY: AN OVERVIEW OF THE NATIONAL CHILDREN'S STUDY

Growing Up Healthy: An Overview of the National Children's Study **is intended for health professionals and researchers, community leaders, child and environmental health advocates, policy makers, Study leadership, and anyone else who is interested in learning more about the National Children's Study.**

This document is a description of the National Children's Study, the largest long-term study of children's health and development ever to be conducted in the United States. This overview provides the framework for the National Children's Study, scheduled to begin in 2006. It outlines the key research questions and introduces the approaches Study leaders will take for involving 100,000 families in the Study over a 21-year period.

Between now and its actual start, National Children's Study planners will complete the process under way to develop the specific details of many aspects of the Study, including design features, research questions, how participants will be selected, and what participation will include. Although the design of the Study is still in development, it is important to share news of this research program—even before all of its components are fully determined—due to the Study's potential and early levels of interest that have been expressed.

THE OPPORTUNITY TO CHANGE THE COURSE OF CHILDREN'S HEALTH

Growing up healthy is every child's right and every parent's dream for their children. As a nation, we have made significant advances in improving child health and development over the past century by identifying the causes of many diseases; by developing preventive measures, treatments, and cures; and by improving the overall health status of our children. Still, children today suffer high rates of asthma, developmental disorders, obesity, preventable injuries, and other problems that continue to confound science and society as a whole.

What is behind the occurrence of these seemingly preventable diseases? What is it about the way we live today that keeps so many children from enjoying healthy lives? A large number of health studies have brought us closer to identifying root causes of diseases, but none to date has undertaken such a comprehensive look at the early lifespan—from prenatal months through young adulthood—with such high hopes for providing answers as the National Children's Study.

The National Children's Study reaffirms the federal government's commitment to the health and well being of children by drawing together the nation's top experts on child health and the environment in an unprecedented collaboration. Multiple federal agencies, national non-profit groups, community health care providers, and more than 100,000 families stand poised to help child health move forward in the 21st century. The goals of the Study complement government efforts to challenge individuals, communities, and professionals to take action to ensure that good health and long life are enjoyed by all. The Study also supports national goals to enhance education, for instance, by exploring the role of children's environments on their readiness to learn.

Undertaking a study of this magnitude will be neither effortless, nor automatic. To be successful over many years, and for tens of thousands of families to participate, the National Children's Study will require a significant mobilization of people, funding, and leadership at all levels. It requires careful attention to privacy, confidentiality, timing for reporting Study findings, and ethical considerations that arise in research involving children. This effort cannot go forward without the enthusiasm of scientists throughout the country, nor can it meet its objectives without the support of local community institutions and organizations.

Participating in the National Children's Study has been compared to planting a tree—the gift the participant provides today may not necessarily benefit the individual, but its value will grow over time, improving many children's lives for years to come. Embarking on a long journey is filled with anticipation and ripe with hope and opportunity for what will be discovered along the way. With the support of the country, the National Children's Study will have the opportunity to give our children the healthy and happy lives they deserve.

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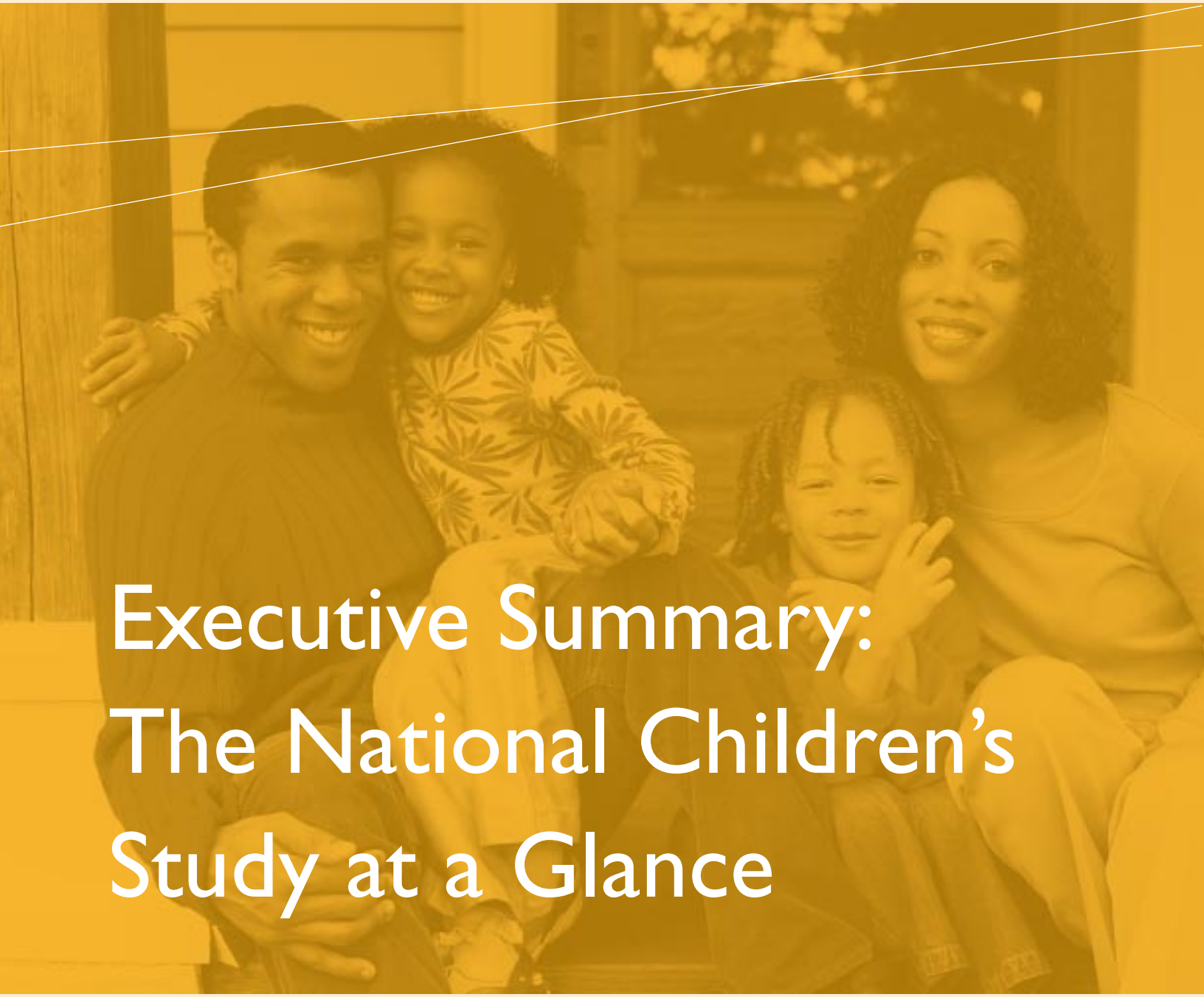


Executive Summary: The National Children's Study at a Glance

WHAT IS THE NATIONAL CHILDREN'S STUDY?

The National Children's Study is a long-term research project that will examine the environmental influences on children's health and development. It will be the largest long-term study of children's health and development ever to be conducted in the United States. The Study will involve 100,000 children, from before birth to age 21, to better understand the link between the environments in which children are raised and their physical and mental health and development. For the Study, the "environment" is defined broadly to include physical surroundings; biological and chemical factors; geography; and social, educational, behavioral, family, and cultural influences. By linking multiple environmental factors to multiple health and developmental outcome measures, the Study has the ability to pinpoint the root causes of many of today's major childhood diseases and disorders, and to determine not only which aspects of the environment are harmful, but also which are harmless or helpful to children's health and development.

WHAT ISSUES WILL THE STUDY FOCUS ON?

The National Children's Study is framed by a set of key scientific research questions that include some of the most pressing health and development concerns for children today. Designed as a longitudinal cohort study, it will examine participants' growth and development over time. The Study will produce information of unprecedented value for scientists, health professionals, and families about multiple concerns in child health and development, including pregnancy-related outcomes, obesity, diabetes, asthma, injury, and social behavior. By incorporating and applying new scientific and information technologies to key research questions, the Study offers the capacity to relate previously unconnected and new data. This unique potential offers hope for new knowledge of and health care approaches to the nation's critical health and environmental concerns.

WHY IS THE STUDY IMPORTANT?

The National Children's Study will provide essential information about many serious health conditions and threats to optimum physical and mental development. The Study will build a valuable data storehouse touching many areas of concern and need—and will even be prepared to answer questions that scientists and the public have yet to ask. Unlike studies that seek answers to a single question, the Study will address multiple questions together to provide as much information as possible. Examples of such questions include: In what specific ways are prenatal exposures to pesticides linked to an increased risk for learning and developmental disabilities? How do viral infections in early childhood influence subsequent development of asthma? How do chemical exposures and social factors interact to affect child development? How do various environmental factors interact with certain genes in children and young adults? And as these interactions occur, how are disease or health altered in the present or later life?

WHY NOW?

A confluence of events points to the need for a study on children's health in the beginning of the 21st century. The Collaborative Perinatal Project—the last major long-term study of American children—took place in the 1960s, and its findings are outdated by technology standards and lifestyle differences. Meanwhile, the rates of obesity, asthma, autism, and some other common childhood diseases and disorders

are on the rise, with no signs of abating. Several studies have pointed to potential causes of conditions such as autism and asthma, but these studies were not large enough to draw more complete conclusions about the complex interactions of environmental, social, and genetic factors that contribute to disease, or about effective prevention strategies.

There is also a societal and economic need for the National Children's Study data. The annual costs to the American economy associated with the priority health and disease outcomes addressed by the National Children's Study currently total in the hundreds of billions of dollars (see page 27). With indicators showing that healthy children have better school attendance, learn better, and are more likely to grow up to be productive workers and family members, now is the time to pursue a long-term study of factors influencing the health and development of the nation's children.

Today's scientists and other researchers are better equipped than their predecessors to undertake the challenges posed by the Study. Technology now exists to collect and analyze the vast amounts of data the Study will deliver. New tools make possible measurements of exposure to many environmental influences. There are now better means to keep participant records safe and confidential. And, with the completion of the human genome sequence in 2003, there is an extraordinary opportunity to analyze the interactions between genetic and environmental factors that affect health.

WHY FOCUS THE RESEARCH ON CHILDREN?

Children are not simply "little adults." Their immature systems often make them more vulnerable than adults to environmental exposures. And young children interact with the environment differently. For instance, they spend more time on the ground, close to dust, soil, and other elements of the environment. Scientists need to know more about many environmental factors and whether they are harmful, harmless, or helpful to children's health and development. Studies conducted with adults often have little application to children. Research findings on the effects of lead on child development or findings of the impact of maternal alcohol use on the fetus highlight the need for concern about environmental exposures and children's developing systems. Past lessons like these form a key rationale for exploring the effects of other potentially serious environmental influences on children.

WHO WILL BE INVOLVED?

The National Children's Study will recruit more than 100,000 women from across the United States who are likely to have a child in the near future. These women will constitute a cross section of ethnic, geographic, and socioeconomic groups and will be representative of the national population. The Study plans to start recruitment in 2006 and expand nationwide in 2007. By including families from varied backgrounds and family structures, the Study can better investigate issues of vital interest to all communities.

WHO IS LEADING THE STUDY?

The National Children's Study will be a collaborative effort involving a host of public and private partners committed to improving children's health. The U.S. Department of Health and Human Services (HHS)—through the National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC)—and the U.S. Environmental Protection Agency (EPA) are leading

the Study. The Study will rely on a consortium of more than 40 federal agencies and departments, as well as on child and environmental advocacy and support groups, private industries and foundations, community leaders, university-based scientists, and local medical sites across the country.

Researchers from each of these entities are participating in advisory and consultative groups and, in some instances, are helping to design and guide the Study. As the Study evolves, the consortium will maintain partnerships to ensure that the Study is addressing the pressing public health problems of the nation. The consortium, together with its partners, will sustain the Study over the next two decades and ensure that all organizations, agencies, and groups are focused on common goals.

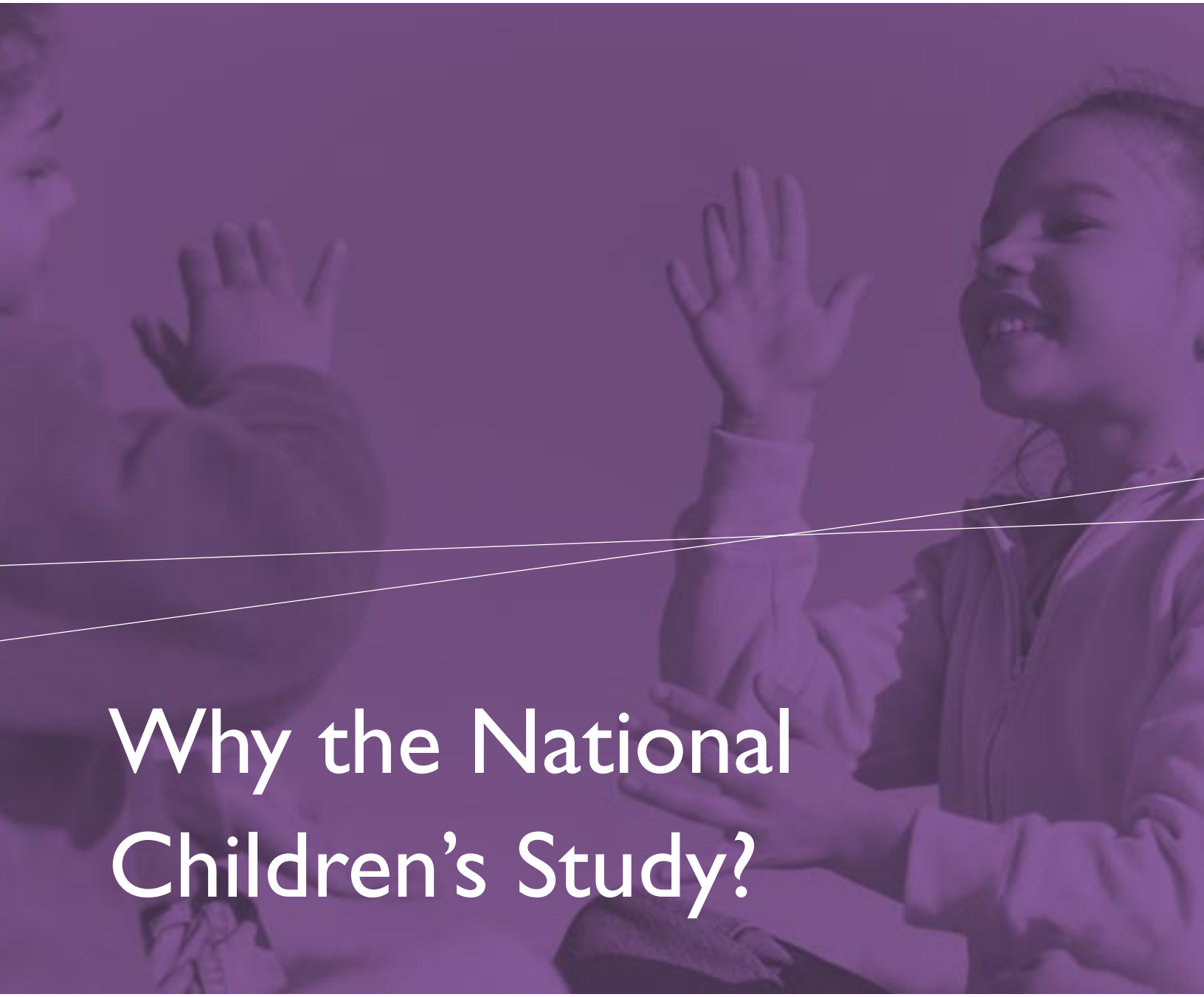
WHAT WILL WE GET FROM THE NATIONAL CHILDREN'S STUDY—AND WHEN?

The National Children's Study will identify early-life exposures that affect individuals before birth, during childhood, and throughout the rest of their lives. It will provide researchers, health care providers, educators, and others who work with children with a resource of data from which to develop prevention strategies, health and safety guidelines, educational approaches, and, possibly, new treatments and cures for health conditions. In addition, the Study will help to prove or disprove many theories of child health and development that are speculative today. For the first time, a Study will allow researchers to apply knowledge of the human genome on a large scale and to understand the conditions that arise from many factors, including gene/environment interactions. It will provide answers to questions about children's health and

development for many years. Researchers will not need to wait for the completion of the Study to analyze the results. Beginning with birth outcomes, findings will become available within two to three years after the Study is launched. Throughout the Study's duration, intermittent results will allow for continued insights.

WHY SHOULD I GET INVOLVED WITH THE NATIONAL CHILDREN'S STUDY?

By supporting the National Children's Study, whether through expertise, communication, community resources, participation in the Study, or other ways, you will be helping to improve the health and well being of children for years to come. The success of the Study rests solely on the participation and support of health care providers, scientists and other researchers, educators, community leaders and liaisons, child health and environmental advocacy and support groups, policy makers, and, of course, those who volunteer to participate in the Study and their families.



Why the National Children's Study?

Fifty years ago, most American children walked to school, rode their bikes without helmets, and ate home-cooked dinners each night with their families. Car travel for children—without seat belts—seldom occurred more than a few times a week. Fewer children were overweight—fewer high-fat snack foods, coupled with more physically active lives, helped to keep them at healthy weights.

But 50 years ago, pesticides were used routinely in our yards and kitchens. Pregnant women were not commonly advised to avoid cigarettes or alcohol. Type 2 diabetes was considered an adult disease. The diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD) did not exist. Physicians rarely treated asthma. Babies were placed on their stomachs to sleep.

In the years since, research has brought about significant improvements in children's health. Today, caregivers are urged to place infants on their backs to reduce the risk of Sudden Infant Death Syndrome (SIDS). Lead has been removed from house paint and gasoline after being linked to reduced IQ in children.[1] Cribs, high chairs, and playground equipment are now safer, and most parents wouldn't even think of transporting their children without car safety restraints.

But with advancements, new challenges have emerged. Children today make less than one in seven trips to school by walking or biking.[2] Although this has sharply reduced childhood pedestrian and bicycle injuries, rates of obesity and overweight among children have tripled since the mid-1960s.[3] Asthma is now the most common chronic disease of childhood.[4] ADHD and developmental disorders collectively are estimated to affect 17 percent—nearly one in every five—school-age children.[4,5] And even though the infant mortality rate in our increasingly diverse society has reached an all-time low, and the proportion of mothers receiving early prenatal care is at a record high, disparities in care and outcomes remain among racial and ethnic groups, presenting a host of challenges for many families.[6]

A CHANGING AMERICA

As many health and safety practices from past generations have been validated or dismissed based on new evidence, we have come to understand that the environments our children live in are profoundly important. From the air they breathe to the food they eat, from where they live to how they live, the environments in which our children grow affect their lifelong health and well being.

Multiple studies point to associations between air pollution and allergens with asthma, poor diet with obesity, and pesticides with impaired neuro-development. Today, these problems stand among the most pressing public health concerns in the United States. Yet, with the prevalence of these conditions remaining stubbornly persistent, or on the rise, few studies can confirm more definitive links that lead to prevention strategies. In addition, with the threats of terrorism, violence, and other stress-inducers becoming facts of daily life for many families, understanding and protecting our children's health and safety is a national priority.

Everyone is worried about the health and education of our children. Parents and grandparents—we all want to do right by our children. We need a scientific base for what we are doing because our children's future is at stake.

Lynn R. Goldman, M.D., M.P.H., professor, Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health

WHY STUDY CHILDREN?

Compared with adults, children:

- Have a greater vulnerability to environmental exposures;
- Have immature mechanisms for detoxification and protection;
- Have several critical windows of vulnerability, especially before birth;
- Have differences in metabolism that cause different reactions to the same exposures; and
- Spend more time on the ground and put objects in their mouths.

COMMON EXPOSURES

The National Children's Study will measure:

- Living conditions and housing: air quality, dust, pet allergens, lead levels
- Family and social experiences: child care, alcohol use, family resources
- Community characteristics: neighborhood safety, access to health care
- Activity and diet: sports, food additives, in-home versus takeout meals

Children are not simply "little adults." Because of differences in both physiology and behavior, what we understand about how adults interact with their environments does not necessarily apply to children. For instance, children tend to be more vulnerable to environmental threats because their developing systems cannot effectively resist and break down toxicants.[7]

In response to growing concerns over children's health and development, a partnership of government, community, advocacy, and private organizations is planning this long-term, observational study of how health and development during the first 21 years of life are affected by physical, chemical, biological, and psychosocial environments.

The environment is defined broadly in the National Children's Study to include natural and man-made environmental factors, biologic and chemical factors, physical surroundings, social factors, psychological influences and outcomes, cultural and family influences, and geographic locations.

The National Children's Study will observe approximately 100,000 children in the United States from before birth to their 21st birthdays, and possibly beyond. The Study seeks to determine not only what is harmful, but what is harmless and helpful to children's health and development. The Study will measure exposures to, and relationships with, an array of environmental factors. Initial research findings will be published soon after the birth of the children. Findings will continue to be published throughout the duration of the Study.

We need to get really basic facts about all these diseases. It all starts in childhood.

William Castelli, M.D., former director, the Framingham Heart Study

The Study will be uniquely positioned to examine and assess a multitude of elements and aspects of participating children's lives, from the constructed world of neighborhoods and schools, to chemical exposures linked to the atmosphere, water supplies, or food, to the interactions of birth history, family patterns, and the frequency and severity of specific diseases. This ability to examine multiple exposures and link them in cause-effect relationships with multiple outcomes is the defining characteristic of the National Children's Study. The Study's trajectory will encompass pregnancy-related influences, including latent or unrecognized prenatal infections, the impact

of maternal diabetes, the interplay of individual genetic inclinations with subsequent behavior patterns, school performance, and the development of conditions such as asthma, diabetes, or obesity.

In the broadest sense, the National Children's Study will provide new insights into human growth and development. Incorporating the powerful reach of the human genome, genetic assays, and new computing technologies will further enhance the Study's power. By implementing various tools of connection and collaboration among biologic, physical, engineering, computer, and clinical sciences, the Study's outcomes promise to be of fundamental importance not only for medical diagnostics and health care, but also for educational strategies, city planning, public policy, and environmental regulation.

PRIORITY FOR OUR TIMES: A STUDY OF HEALTH OUTCOMES AND EXPOSURES

The rationale for the National Children's Study stems from a consensus within the research community that new and reliable data on factors responsible for child health are needed. Previous studies established vital scientific foundations, including some information about genetic susceptibility to certain diseases. But no study to date has been broad enough or long enough to draw definitive conclusions to many outstanding child health and development questions.

The National Children's Study has relied on many of the world's foremost scientists in designing and developing the plan of research.

In formulating the National Children's Study's key areas of emphasis, hundreds of scientists and representatives from community and professional organizations helped to identify and articulate important children's environmental health questions. These core hypotheses encompass many important child health outcomes and exposures that are best studied for long-term follow-up and this particular research design. They establish both a scientific framework as well as a "public identity" for the National Children's Study.

The National Children's Study Interagency Coordinating Committee used the findings from 20 National Children's Study working groups, as well as reviews of children's environmental health literature

With its emphasis on multiple health outcomes and environmental exposures among a cohort of 100,000 children, the National Children's Study combines scientific power and cost-effectiveness. By evaluating data across exposures, the Study will help create a complete picture of what actually causes diseases and influences health.

The National Children's Study will help public health practitioners develop effective prevention and intervention strategies to improve the health of children and adults, and will assist doctors and health care professionals in better diagnosing and treating diseases in the future.

and comments from a broad-based Study Assembly to develop initial hypotheses. Although the hypotheses ensure that specific research areas will be included in the Study, they do not, by themselves, convey its true breadth. The full scope of the Study encompasses these hypotheses in tandem with the priority outcomes and exposures outlined below. Together, they represent an approach to addressing the nation's most urgent public health concerns.

PRIORITY HEALTH OUTCOME THEMES

Pregnancy-Related Outcomes. Can good nutrition help overcome potential risks from other environmental exposures that can affect the fetus? How does infection at various times over the course of pregnancy impact the fetus?

Injury. What are the links between childhood injuries and risk-taking behaviors? How do city and neighborhood planning and construction encourage or discourage injuries? How do genes and the environment interact to promote or prevent violent behavior in teenagers? How do innate characteristics, parenting, and peer relationships influence risk taking, persistent aggression, and risk of injury?

Asthma. What really causes asthma and how can it be prevented? Can very early exposure to some allergens actually help children remain asthma-free? How do the multiple factors contributing to asthma interact to result in the disease?

Obesity, Diabetes, and Physical Development. Are lack of exercise and poor diet the only reasons many children are overweight? How do genes and the environment interact to encourage obesity? How do social, behavioral, and family factors that affect the development of dietary preferences and physical activity patterns in early childhood determine the risk of childhood obesity?

Child Development and Mental Health. How are exposures to environmental toxicants, stress, pre-natal nutrition, and other factors, such as genes, linked to a child's risk of autism, ADHD, and other developmental disorders?

We are pleased that the goals of the proposed national study will encompass our basic mission of understanding the complex components of adverse birth outcomes, including birth defects, prematurity, and low birth weight, as a critical route to improving child health.

Nancy Green, M.D., medical director,
March of Dimes

FROM EXPOSURE TO OUTCOME

Understanding Complex Interactions in a Child's Environment

A broad range of possible exposures must be examined to pinpoint causes of the potential outcomes. The National Children's Study is uniquely positioned to uncover these complex interactions to address today's health concerns and also those of tomorrow.

GENETICS

In what ways do environmental factors intersect with genes? How do mutations and variations in genes affect the development of diseases?

PRIORITY EXPOSURES

The five priority environmental exposure groups discussed below may have a profound influence (either beneficial or deleterious) on child health and development.

Physical Environment. Do aspects of the physical environment, such as housing quality and neighborhood and community conditions, affect child health and development? What about the influence of physical factors, such as radiation (e.g., electromagnetic, ultrasound, microwave, X-ray), as well as light and noise?

Chemical Environment. What happens to the human organism after long periods of low-dose exposure to chemicals, pesticides, and herbicides? What are the health effects associated with complex low-level exposures?

Psychosocial Environment. How do school environments, emotional stress, family conflict, and personal relationships affect the physical and mental health of children?

Biologic Environment. How do bacteria, viruses, toxins, and diet influence immunity, inflammation, and diseases, such as diabetes? Do infections impact developmental progress, asthma, obesity, and heart disease? How do molecular and genetic mechanisms interact with viruses and bacteria in the expression of disease?

If the Study finds significant effects of chemicals on health, we can enhance our risk management of chemicals and other environmental influences and make changes.

Lee Salamone, director, Public Health Team, American Chemistry Council

STUDY MODEL—THE NATIONAL CHILDREN'S STUDY IS:

The largest proposed longitudinal study of U.S. children, their families, and their environment	A study of children's physical, social, cultural, behavioral, and chemical environments	Hypothesis-driven: focusing on causes of obesity, injury, developmental disorders, asthma, and pregnancy-related outcomes
National in scope: involving children from diverse ethnicities and socioeconomic backgrounds	Large enough to identify causes of important, but less common diseases and conditions	
	The first nationwide children's study to benefit from human genome mapping	Using state-of-the-art technology to capture data and track developments
A national resource for future studies	A public-private partnership of government, private industry, and community organizations	Scheduled to announce first findings in 2008–2009

INTEGRATING PRIORITY OUTCOMES AND EXPOSURES

The outcome themes and exposures will define the Study's parameters over time. The interplay of these factors will help link exposure data to a broad range of health and disease measures. The overall goal is to build a rich source of data to answer the critical public health questions confronting Americans today and in the future.

WHAT PARTICIPANTS WILL BE ASKED TO DO

The National Children's Study will recruit women who are pregnant, or who may soon become pregnant, to assess fetal and maternal health. It will also observe participating children and their families as they grow and live.

Unlike a clinical trial, in which participants take medication or engage in a prevention or treatment activity, an observational study like the National Children's Study collects information about participants' lifestyles in the home, at school, and at play. Families will visit a participating Study site on a few occasions during the baby's first year of life and less frequently in subsequent years. During the visits, health professionals will collect samples such as urine, blood, hair, DNA from parents and grandparents, and other information regarding the child's environment and health status. Families can expect to receive information about the research findings from Study coordinators by phone, mail, and the Internet, and through home visits. In home visits, a nurse or health research assistant will confer with the parents or caregivers to collect samples of indoor and outdoor air, water, or other environmental components.

The Study will be implemented through a group of university hospitals, community hospitals, local health clinics, or physicians' offices across the country. Participants will be recruited by local members of the Study team and will participate in or near their hometowns. Study planners are designing a careful recruitment strategy and follow-up plan to keep families actively engaged in the Study for more than two decades—no small challenge in today's mobile society. The National Children's Study will promote its research results through scientific journal articles, Web site postings, and media outreach activities.

A UNIQUE PARTNERSHIP

The National Children's Study is a collaborative effort led by the U.S. Department of Health and Human Services (HHS)—through the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC)—and the U.S. Environmental Protection Agency (EPA). Operating through the NIH's National Institute of Child Health and Human Development (NICHD), the Study benefits from the input of more than 40 other federal agencies and departments. Study planners hope to build partnerships among local communities, health care providers, and federal and non-federal scientists, as well as parent, advocacy, and private industry groups that will inform the Study throughout its duration and will ensure the greatest benefit to the nation's children.

The National Children's Study has the potential to fill knowledge gaps, make a positive impact on the lives of children and adults, and generate the knowledge to find cures and maintain healthy lives. Everyone involved—families, researchers, policy makers, and the children themselves—will offer a gift to future generations through their support of and participation in the Study.

The benefits of the National Children's Study will extend far beyond the U.S. borders. What is learned about American children and their environments can help people around the world.

The Genesis of the National Children's Study: Children's Health Act of 2000

By the late 1990s, numerous experts in science and medicine were calling for new data on children's health and development. The last major study of children's health, the Collaborative Perinatal Project (1959–1974), offered information that reflected very different physical environments and social settings, and a far less diverse population of children. Studies conducted since, although offering important insights, have been too small or too specific to analyze the wide range of environmental factors and relationships that the National Children's Study will address.

With many childhood diseases and unhealthy conditions on the rise over the past two decades, support has grown for a broad partnership of agencies to join forces in conducting an extensive study of children's health. Such a study would develop an important data resource and would yield powerful clinical and research tools at a substantial cost savings over separate studies conducted by individual agencies.

CONGRESSIONAL COMMITMENT

In 1999, the President's Task Force on Environmental Health and Safety Risks to Children recommended a large, new longitudinal study of children to fill large gaps in knowledge about environmental effects and children's health and about how to address these effects. The Task Force's recommendation to initiate a new study was quickly followed by congressional passage of the Children's Health Act of 2000 (Public Law 106–310). Among other provisions, this act authorized the development of the National Children's Study. President George W. Bush has twice reauthorized the Task Force, and Congress has demonstrated continued interest in the National Children's Study by requesting briefings on Study plans and expected outcomes.

The President's Task Force on Environmental Health and Safety Risks to Children was established in 1997 by executive order. The Task Force was instrumental in highlighting the need for the National Children's Study, and its members from 16 departments and White House offices continue to be a strong source of support.

The Children's Health Act called for the Study to be directed by a consortium of agencies led by the NICHD in partnership with CDC and EPA. The National Institute of Environmental Health Sciences (NIEHS) and many other federal partners concerned about children's health and the environment have joined these three lead agencies.

Congress has demonstrated continued support for the National Children's Study since passing the Children's Health Act of 2000.

An Interagency Coordinating Committee, comprising scientists from each lead agency with oversight by the NICHD director, was formed to guide the Study's planning and implementation. A federal advisory committee and 20 working groups composed of federal and non-federal scientists and other representatives have made substantial progress informing various aspects of the Study.

Initial funds for fiscal years 2000 through 2004 were contributed by the lead agencies. Congress has also remained supportive, as reflected by language in appropriations committee reports. Numerous interagency partnerships have been established to plan the components of this ambitious long-term study and to conduct pilot studies.

Economic Investment in Health Research: Better Health, Better Returns

A research undertaking of the magnitude of the National Children's Study raises immediate economic questions. How much does a study of this size cost? What is the true "return on investment" in terms of the nation's health and economy?

New findings in medical research make the news every day, be it gene therapy, bionic hearts, the regeneration of nerve cells, or the latest breakthrough in real-time medical imaging. As discoveries become practical tools, they help confirm that funding for medical research is a sound investment. But at this start of a new century, biomedical research is facing some of its most significant challenges. Although the goals of health research are clear—realizing health benefits for all people—the debate over cost continues in all quarters, from health care professionals and researchers to policy makers, educators, and concerned citizens.

RESEARCH AS AN INVESTMENT

A useful way to consider benefits of health research is in terms of "health care costs saved." A 1995 report from the *Federation of American Societies of Experimental Biology Journal* estimated that $68 billion in annual savings are attributable to medical research due to reduced or avoided hospital stays, or new and improved advancements in medications and medical procedures.[8] The report concluded that for every research dollar invested, two to three dollars are returned to the economy.

Specific economic advantages of the National Children's Study—which is projected to cost an average of $100 million per year, or $2.7 billion over 25 years—can be viewed from the perspective of direct cost reduction. Five of the Study's major health outcome theme areas encompass diseases and conditions that currently create a societal burden of more than $750 billion per year.[9-15] This figure is all the more troubling because it represents both treatment and intervention for conditions that research has shown can be mitigated and possibly prevented.

Previous studies, similar in some ways to the National Children's Study, have demonstrated significant economic benefits. For instance, groundbreaking 1970s research on the effects of lead on children's neurodevelopment prompted the phasing out of lead in gasoline, paint, and other products.[16] It has been estimated that the economic gain from this change is between $110 billion and $319 billion among each year's cohort of two-year-old children in terms of expected lifetime earnings.[17] Studies that found a link between low folate intake and neural tube defects resulted in food supply fortification and recommendations for women to take vitamin supplements as prevention strategies.[18] These measures have produced tangible economic benefits as well; for example, the annual net economic benefit of fortification has been estimated to be $94 million.[19]

In addition to health care costs saved, an important but less quantifiable economic aspect is human potential realized due to optimal health. Healthier children have greater school attendance, learn better, and are more likely to grow up to be productive workers and family members. By generating findings that can help children grow into healthy and dynamic adult members of society, the National Children's Study will yield a valuable "return on investment." What we have now, as a result of the Framingham Heart Study, is a powerful link between scientific data and health care practice. In mounting a complex, multifaceted, collaborative medical study involving thousands of participants, Framingham researchers not only broke new ground, but also learned that research provides benefits that can only be partially understood when a study begins.

A sustained research effort would greatly improve the understanding of diseases and could stimulate innovative strategies to limit the impact of conditions, ultimately reducing the nation's health care costs.

ANNUAL COST TO THE UNITED STATES FROM DISEASE BURDEN

Injury **$480.5 Billion[a]**		**Obesity** **$117 Billion[b]**
	Diabetes **$132 Billion[c]**	**Asthma** **$14 Billion[d]**
Neurobehavioral Disorders **$9.2 Billion[e]**		**Low Birth Weight** **$6 Billion[f]**
		Total **$758.7 Billion[g]**

Note: The above figures are adopted from a range of sources that may have used varying methods and assumptions in calculations.

a. National Safety Council. (1999). *Report on injuries in America* [Electronic version]. Retrieved November 17, 2003, from http://www.nsc.org/lrs/statinfo/99report.htm

b. Centers for Disease Control and Prevention, DHHS. (n.d.). *Improving nutrition and increasing physical activity* [Electronic version]. Retrieved October 12, 2004, from http://www.cdc.gov/nccdphp/bb_nutrition/

c. American Diabetes Association. (2003). Economic costs of diabetes in the U.S. in 2002. *Diabetes Care, 26*(3), 917-932.

d. American Lung Association. (2003, March). *Trends in asthma morbidity and mortality* [Electronic version]. Retrieved October 21, 2004, from http://www.lungusa.org/atf/cf/%7B7A8D42C2-FCCA-4604-8ADE-7F5D5E762256%7D/ASTHMA1.PDF

e. Landrigan, P. J., Schechter, C. B., Lipton, J. M., Fahs, M. C., & Schwartz, J. (2002). Environmental pollutants and disease in American children: Estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. *Environmental Health Perspectives, 110*(7), 721–728.

f. Lewitt, E. M., Baker, L. S., Corman, H., & Shiono, P. H. (1995). The direct cost of low birthweight. *The Future of Children, 5*(1), 35–56.

g. Silverstein, S. C., Garrison, H. H., & Heinig, S. J. (1995). A few basic economic facts about research in the medical and related life sciences. *The Federation of American Societies for Experimental Biology Journal 9*(10), 833–840.

A Tradition of Landmark Studies

Several major studies have used a longitudinal (following people over time) design, including the landmark Framingham Heart Study launched after World War II. These studies—four of which are ongoing—take advantage of observations unfolding over many years to better understand the development of certain diseases and conditions.

The Collaborative Perinatal Project, launched in 1959 by the NIH's National Institute of Neurological Diseases and Blindness (now the National Institute of Neurological Disorders and Stroke), followed more than 40,000 pregnant women and their children until 1974. The study contributed some of the most important information ever collected on rubella during pregnancy,[20] as well as some of the first understandings of the effects of fetal exposure to alcohol and lead. It also demonstrated that febrile seizures in infancy do not demand treatment and improved our understanding of cerebral palsy. The Collaborative Perinatal Project was one of the first studies to yield insights on SIDS.[21] Data from the study created an important resource on many children's health issues, including the impact of pregnancy outcomes and the effects of social and economic variables on the health of individual children.

The Framingham Heart Study is the longest-running U.S. study involving a large number of participants (57 years with more than 10,000 participants).[22] Launched in 1948 under the auspices of the NIH's National Heart Institute (now the National Heart, Lung, and Blood Institute), the Framingham Heart Study is the prototype for longitudinal medical studies. It identified cigarette smoking, overweight and obesity, elevated cholesterol and blood pressure levels, and lack of exercise as risk factors for heart disease.[23-27] The challenges accepted by the study's originators have long since translated into significant health improvements for people around the world,[28] and literally billions of dollars have been saved through reduced health care costs.[29]

The findings from the Framingham Heart Study revealed that high blood pressure is a risk factor for stroke as well as heart disease (1961, 1970); that women's risk for heart disease increases after menopause (1976); and that psychological and social factors have profound effects on heart health (1978).[30]

The Bogalusa Heart Study, the longest and most detailed children's heart health study, was launched in 1972 and is scheduled to end in 2005. Focusing on participants from birth to age 31, it has confirmed that high blood pressure and heart disease can begin in childhood (with documented effects as early as age five), and that the nature of heart disease risk factors among children differs from that of adults. The study has also validated connections between environmental factors and overweight, obesity, elevated cholesterol, and blood pressure levels in children.[31, 32]

[The] Framingham [Heart Study] gave us the link between diet and heart attacks, between stroke and cholesterol. The findings translated immediately to the medical community. Doctors stopped smoking and told their patients to stop too. Big studies are costly but yield enormous benefits.

Phil Landrigan, M.D., M.Sc., professor and chairman, Department of Community and Preventive Medicine, Mount Sinai School of Medicine

The Nurses' Health Study, launched in 1976, looked at the risk factors for major chronic disease in women. The Nurses' Health Study II was launched in 1989 as a long-term evaluation of the effects of oral contraceptives, diet, and lifestyle factors on women's health. Each study has involved more than 100,000 nurses and has verified that heart disease risk is reduced among women who take a daily multivitamin; that women who eat certain types of fish on a regular basis have a lower incidence of heart disease; that healthy lifestyles significantly lower the incidence of heart disease; and that cigarette smoking is associated with increased heart-disease risk, particularly among women with diabetes.[33]

The Women's Health Initiative, launched in the mid-1990s, is an observational study of 150,000 postmenopausal women between the ages of 50 and 79 over a 15-year span. The study focuses on hormone therapy (HT), diet, calcium, and Vitamin D supplementation, and the relationships of these

factors to heart disease, breast and colorectal cancer, and osteoporosis. The Women's Health Initiative has already offered insights on estrogen plus progestin HT, noting that this particular type of therapy is associated with an increased incidence of stroke and dementia.[34]

As each of these major studies demonstrates, size and complexity are necessary to reveal the intricate patterns of human biology, as well as the subtle relationships between causes and effects that can be expressed as diseases. These multifaceted research efforts, which involve thousands of participants, continue to provide keys to medical knowledge and clinical care, as they remind us of the powerful links between scientific data and health care practice.

The Collaborative Perinatal Project taught us that the major causes of cerebral palsy occur earlier in pregnancy than the time of birth. This study found that inflammation of the placenta is a major cause of pre-term birth and found it 25 years before the idea came to be popular in the 1980s. The study was also very influential in how we manage jaundice in babies, even today.

Mark Klebanoff, M.D., director, Division of Epidemiology, Statistics, and Prevention Research, NICHD

Studying an Increasingly Diverse Nation of Children

Closing the gaps in health among the nation's children is among the federal government's highest health priorities. In its efforts to promote health and prevent disease, the government seeks to ensure that all Americans benefit equally from advances in quality of life. It also seeks to eliminate health disparities, specifically those based on gender, race, and ethnicity; income and education; and disability. The nation recognizes that, although great strides have been made in addressing health disparities, much work remains.

The Children's Health Act of 2000 calls upon the National Children's Study to involve diverse populations, and to assess health disparities among the nation's children. The Study will help uncover differences among groups of people in terms of health, health care access, and disease rates, allowing disparities to be identified and addressed. The Study participants will be as representative as possible of the overall U.S. population at the beginning of the 21st century—a population much more diverse than even a decade ago, and becoming more so each year.

Sociodemographic characteristics offer a compelling portrait of the nation's children in a time of growing diversity and enhanced risk of disease among a range of ethnic groups. Over the last decade the African American population increased faster than the total population,[35] and Hispanics became the nation's largest ethnic minority group[36] (with Hispanic children accounting for one of every six children in the United States[37]). Meanwhile, the percentage of Asian American/Pacific Islander children doubled (from 2 percent to 4 percent) in the last 20 years.[38]

But despite vigorous population growth, many American children today face significant health challenges related to an array of factors. Some children confront poverty and poor access to health care, as well as violence, language barriers, and exposures to air and water pollution. In growing numbers, they also face diseases—such as diabetes and heart disease—exacerbated by high-fat diets and lack of physical activity.

A few select facts underscore the pressing need for greater knowledge about the health and well being of our nation's children. Mexican American boys are most affected by obesity. Puerto Rican children have the highest prevalence of asthma—11 percent—of any U.S. ethnic group.[39, 40] African American children are more likely to live in poverty than their white peers.[41, 42] And African American adolescents succumb to violent death at a homicide rate six times higher than that of white adolescents.[43] Type 2 diabetes is a growing problem for American Indian/Alaska Native adolescents, who have the highest rates of any U.S. ethnic group.[44,45] This population is also suffering from depression and substance abuse disproportionately, with a suicide rate 1.5 times the national rate.[46,47] In addition, American Indian/Alaska Native infants are unduly burdened by Fetal Alcohol Syndrome, with an incidence at least twice the national average.[48]

A major challenge [in the Study] will be having a balanced sample representing the U.S. as it is now. You are going to see emerging populations over the next 20 years. The Latino population and other ethnic groups are growing extremely fast, and we are going to have to account for the changing demographics of the United States.

Tom Curtin, M.D., chief medical officer, National Association of Community Health Centers

By mounting a broad-scale investigation of our increasingly diverse nation of children, the Study can learn from the socioeconomic and health successes of the last two decades. For example, over

Closing the gaps in health among the nation's children is among the federal government's highest health priorities.

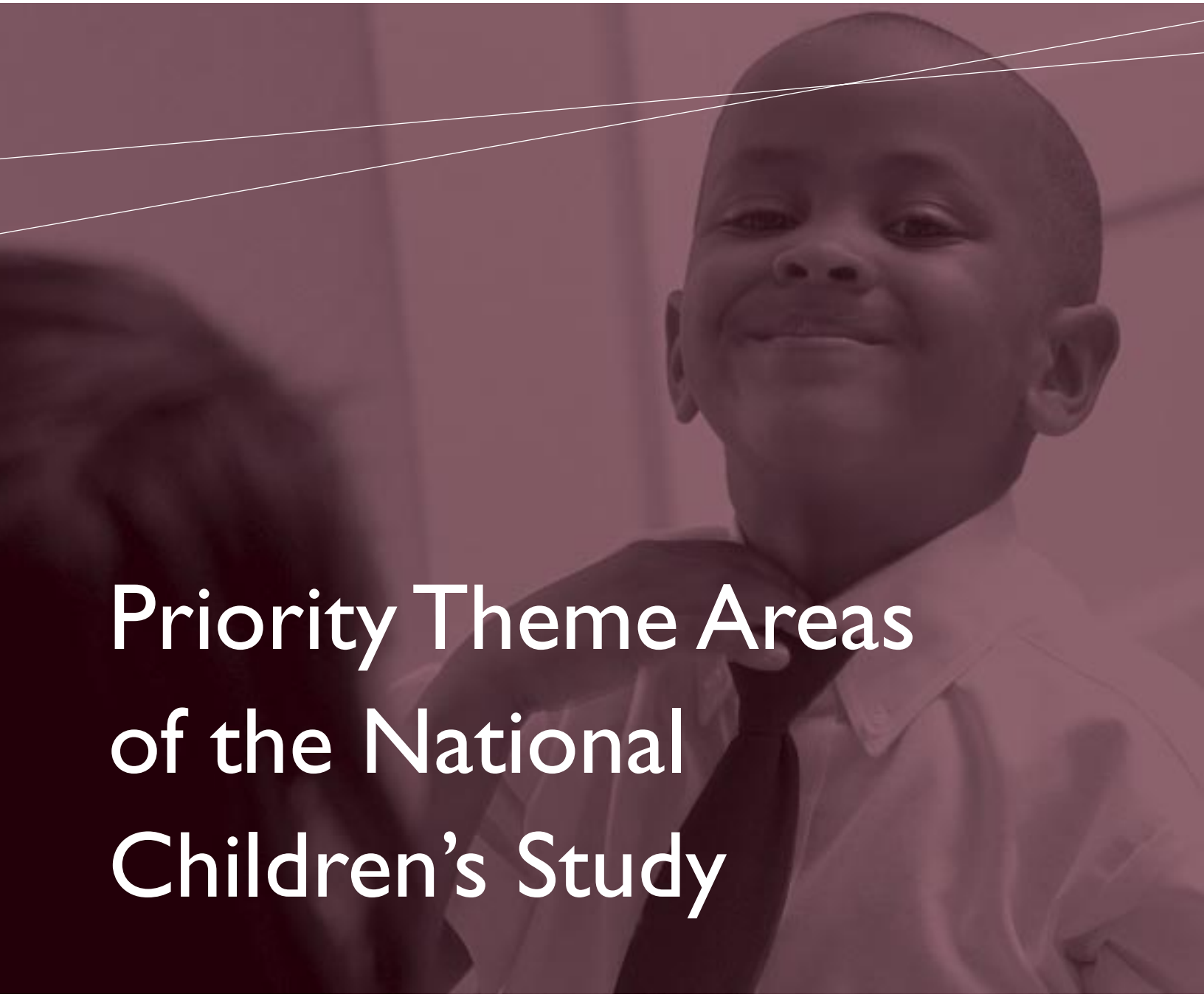
NATIONAL POPULATION ESTIMATES FOR CHILDREN UNDER AGE 18

Reporting One Race	Number of Children
White	55,920,453
African American	11,355,348
American Indian/Alaska Native	874,416
Asian	2,772,235
Native Hawaiian and Other Pacific Islander	148,927
Reporting Hispanic or Latino Origin*	
Hispanic or Latino	13,588,755

* U.S. Census Bureau population estimates as of July 1, 2003. The U.S. Census considers race and Hispanic origin two separate concepts and therefore Hispanics may be of any race or races. Source: U.S. Census Bureau (2004). *National population estimates characteristics* [Electronic version]. Retrieved September 22, 2004, from http://www.census.gov/popest/national/asrh/NC-EST2003-asrh.html

the last 20 years there have been significant gains in the number of Hispanic middle-class households,[49] and today more than half of African American married couples have incomes higher than $50,000.[50] Improved birth weights are evident among Hispanic infants, and their mortality rates are close to those of non-Hispanic white infants.[51] Infants born to Asian American/Pacific Islander mothers have the lowest infant mortality rate of any U.S. ethnic or racial group overall.[52] In addition, low birth weight babies are less common (6.0 percent) among American Indian/Alaska Natives than all children combined (the national rate is 7.3 percent).[53]

By adding to and analyzing these kinds of data more comprehensively than ever before, the National Children's Study can develop the insights needed to answer pressing questions about the full range of racial, ethnic, and socioeconomic contexts that compose the national fabric. The Study will bring a unique and balanced power to the examination of diversity. To realize this opportunity fully, the Study will seek the participation of a varied group of families—particularly the women and children—as pivotal contributors. To ensure that health disparities are adequately addressed, the National Children's Study will recruit extra participants from some diverse populations. Study coordinators will identify women through multiple venues, from doctors' offices and community clinics, to social service and community groups. Study information will be disseminated through many outlets, including churches, libraries, retail outlets, and community centers. And, because participant retention can be more difficult for families dealing with poverty, transportation problems, and geographic isolation, the National Children's Study will develop ways to make participation easier for them.



Priority Theme Areas of the National Children's Study

The National Children's Study will address a range of research questions that encompass the most critical child health issues of our time. Although some of these concerns have been examined in other studies, no scientific study to date has carried the scale and scope of the National Children's Study, or the ability to assess interactions among many exposures and related health outcomes in a large population of children.

By using a trio of key features—time (20-plus years), number of participants (100,000), and the array of scientific tools now available to investigators—the National Children's Study will be able to deliver new perspectives on many of the nation's most pervasive child health questions. With new analytical techniques brought to bear, such as DNA microarrays ("gene chips") and high-speed processing of biological samples, the Study will seek to address the exposures and conditions that represent the most significant risks and burdens to U.S. children.

At the heart of this objective is the Study's unique capacity to evaluate multiple exposures in varying concentrations and combinations across two decades, and to link those findings with multiple outcomes. This capacity can help reveal the many ways that exposures are expressed in children over time, from congenital anomalies to behavioral variations to diseases that are common to specific settings or environments.

Today, the number of childhood conditions with suspected environmental connections comprises a daunting list. There is compelling evidence that obesity, cancer, asthma, autism, birth defects, and cerebral palsy all carry significant environmental linkages.

In meeting the challenge to create a large-scale database, the National Children's Study will respond to the evolution of scientific thinking across the next 20 years, including improvements in data collection, as well as innovations in various research tools and techniques. Most important, though, the Study will center its efforts around a number of broadly defined health outcome and exposure themes that are considered to have the greatest overall impact on child health and development. Some of these issues include obesity, diabetes, and physical development; injury; asthma; pregnancy-related outcomes; outcomes related to child development and mental health; exposures to psychosocial, physical, chemical, and biologic environments; and the influence of genes and genetic variation on environmental exposures. By maintaining broadly defined areas of interest, the Study preserves the flexibility to respond to new and unforeseen questions as they arise.

Even with approximately 100,000 children enrolled, the National Children's Study cannot directly address every disease or condition; this is particularly true of rare conditions affecting very small portions of the population that are better served by dedicated case-control studies. The breadth of the data to be collected signifies how valuable it will be for learning about even these rarer conditions. Using the organizing principle of interrelated "priority theme areas," the National Children's Study will optimize the research effort across a variety of health concerns, generating a powerful scientific resource that can shed unexpected light on new questions for years to come.

The following discussions highlight several priority theme areas, outlining the basic nature of the public health challenges in each case. In offering key questions that might guide investigators, a number of promising approaches and strategies emerge. The avenues of investigation are too numerous to cite each and every possibility, but a number of specific Study questions have been developed to ensure that key measures are obtained, and that the sample of participants and study design are adequate for the questions to be addressed.

Among other things, the National Children's Study will provide us with critical information on the relationship between housing and health and [will] improve our understanding of the association between the built environment and autism, respiratory ailments, obesity, childhood injury, and other areas that concern us all.

Peter J. Ashley, Dr.P.H., environmental scientist, U.S. Department of Housing and Urban Development, Office of Healthy Homes and Lead Hazard Control

PREGNANCY-RELATED OUTCOMES

Maternal and infant health has improved dramatically in the United States over the last century. The infant mortality rate continues to decline; the number of pregnant women who smoke cigarettes continues to fall; and birth rates among teenagers in all ethnic groups declined throughout the 1990s and continue to do so today.[54] But despite these successes, the United States lags behind 27 other industrialized countries in infant mortality, and the root causes of pre-term birth remain unclear.[55] And disparities exist among racial and ethnic groups, such as African Americans, for whom the infant mortality rate is more than double that of white children.[56]

Addressing Pregnancy-Related Outcomes

The National Children's Study will investigate a range of important research questions related to pregnancy and events that occur within one year after the end of pregnancy, including birth defects, low birth weight, pre-term births, miscarriage, stillbirth, and neonatal problems. Some research questions include:

Does impaired glucose metabolism during pregnancy increase the risk of birth defects? Evidence suggests an increased risk of birth defects among children born to women who are diabetic before or during pregnancy.[57] The Study will assess the presence of impaired maternal glucose metabolism, a diabetes precursor, as early as possible in the course of pregnancy. Children born to women with this condition will be comprehensively assessed for evidence of birth defects. Results from this effort can help revise standards of care for prenatal screening, as well as inform guidelines for the management of diabetes during pregnancy.

Is pre-term birth caused by inflammation and infection? Evidence of intrauterine infection is present in up to 40 percent of all spontaneous pre-term births and up to 75 percent of those that occur before 32 weeks' gestation.[58, 59] Recent reports have also linked pre-term births to maternal tooth and gum disease, and to inflammation in other parts of the body.[60] The Study can collect cervical and vaginal cultures and histological material as early in pregnancy as possible to assess for local and systemic inflammatory markers. At birth, placental material and umbilical cord blood can be examined for indications of infection and inflammation. Linkage to obstetric records may provide other evidence of infection to help answer this question.

INJURY

Like infections, injuries require the proper host (the child), vector (transmission of energy to the child by a car or other object), and environmental variable (e.g., lack of smoke detectors). Traffic, swimming pools, staircases, weapons, fire, and household poisons pose the greatest threats to a child's safety, yet are common presences in many children's lives.[61, 62] Injuries are the major cause of death in children after their first birthday.[63] Nearly 10 million children sustained injuries that necessitated medical care in 2001 alone, with some of the most affected survivors being those with a traumatic brain injury, which can affect their cognitive, emotional, physical, and social abilities for the rest of their lives.[64, 65]

Addressing Injury

Past studies on the causes of childhood injuries have provided data needed to pass informed laws and develop proactive interventions, such as free smoke detector programs and child safety caps on medicine bottles.[66, 67] By identifying groups at increased risk due to genetic and other factors, the National Children's Study aims to build upon this knowledge base to inform interventions for subgroups of children at greatest risk of injury. Potential research questions concerning injury include:

How do innate individual characteristics, such as resting heart rate or biologic level of reactivity and other genetic traits, along with parenting and peer environments, influence risk taking, aggressive behavior, and unintentional injury? Improved understanding of biologically based measures of reactivity in infancy holds great promise for insights into why some individuals exhibit high-risk behaviors, while others do not. Animal studies on the interaction of genes and environment in shaping behavior offer a strong foundation for observing similar elements in children—and for pointing the way to science-based injury-prevention programs.

Does repeated head trauma adversely affect neurodevelopment? Although the classic setting for repeated head trauma is athletic competition—with sports-related injuries accounting for some 20 percent of the 1.5 million traumatic brain injuries sustained annually—normal childhood activities also provide ample opportunity for repetitive, mild head trauma.[68] The Study can consider traumatic brain injuries of varying severity based on interviews, school and medical records, and sports participation data and can assess the resulting neurodevelopmental changes.

ASTHMA

Asthma, the most common chronic disease of childhood, is also one of the most costly diseases, affecting around 5 million children in the United States.[69, 70] Between 1980 and 1994, the incidence of asthma increased 74 percent among U.S. children ages five to 14, and it has yet to peak.[71] With nearly 8 percent of school-age children suffering from it, asthma ranks as the most common cause of illness-related school absenteeism.[72]

Asthma's rise has been attributed to a variety of influences such as increased air pollution, and environmental endotoxins, such as soil and pet dander. Increased obesity may also be a factor.[73] Certain asthma-promoting genes are believed to be affected by environmental exposures, particularly in early life. There is some evidence that dust mites, cockroach allergens, and tobacco smoke can cause asthma, but more research is needed to examine a variety of early-life airborne exposures that may be related to the onset of asthma.[74]

Addressing Asthma

Several research questions for the National Children's Study address the possible influence of fetal or early-life exposures on subsequent risk of asthma, including:

Does indoor and/or outdoor air pollution cause asthma? There is clear evidence that air pollution exacerbates asthma, but whether unhealthy air initiates asthma is less certain. The National Children's Study can estimate exposure to specific indoor and outdoor air pollutants by sampling air quality in and around participants' homes and schools, through activity diaries, using personal air samplers for some participants, and linking to existing data about outdoor air.

Is early-life infection associated with asthma risk? Some studies have suggested that early-life infections protect against asthma, while others conclude the opposite.[75] To confirm or deny the relationship of infections and asthma, early exposures to infectious diseases can be investigated through family interviews, illness histories, blood tests, day care attendance, and the number of siblings. The Study can collect maternal and umbilical cord-blood samples to assess exposures to infectious agents, conduct interviews with parents and caregivers, and possibly review medical records. In addition, biologic samples can be collected to evaluate immune response and inflammatory factors. The Study can best contribute to knowledge in this area by studying subgroups of children and the interactions among many different exposure and outcome factors.

Does a vitamin-rich diet help decrease asthma risk? Data from CDC's third National Health and Nutrition Examination Survey (1988–1994) note that children exposed to second-hand smoke face exacerbations of asthma.[76] Although further research is required, there is epidemiological data to suggest that dietary antioxidant supplements (e.g., beta carotene, selenium, Vitamin C) might reduce the prevalence and severity of asthma in some children.[77, 78] The National Children's Study can employ multidisciplinary capacities in evaluating children's diets, use of nutritional supplements, and exposure to second-hand smoke. Antioxidant levels can be tested through serum samples and, in some cases, breath analyzers.

OBESITY, DIABETES, AND PHYSICAL DEVELOPMENT

According to CDC, since the 1970s, the proportion of overweight children between the ages of six and 19 has tripled—an increase so rapid that by 2000, the CDC declared obesity a U.S. "epidemic."[79-81] Overweight children have a three-fold higher risk of developing hypertension than children who are not overweight, and three-fourths will grow up to be overweight adults.[82, 83] Health conditions associated with overweight and obesity in children parallel those in adults, such as hypertension, Type 2 diabetes, and psychosocial consequences.[84] Some 20 percent of new Type 2 diabetes is in children between the ages of nine and 19 (a condition that was, until only recently, seen only in adults). In 2002, investigators working with a small cohort demonstrated that impaired glucose tolerance—the "early warning sign" of impending diabetes—is associated with overweight and obesity in children.[85] The National Children's Study can follow up on this finding in a much larger population of children, evaluating the links between and among biology, psychosocial environments, diet, exercise, and obesity.

Addressing Obesity, Diabetes, and Physical Development

The National Children's Study will address several research questions in this area. Some examples include:

Does impaired maternal glucose metabolism during pregnancy cause overweight in children? A number of factors affect glucose metabolism in pregnancy, including maternal nutrition, physical activity, and infection—and the timing of such factors during gestation may be critically important. This question is especially relevant because more women of reproductive age are overweight, a known risk factor for gestational diabetes, and preliminary evidence suggests a relationship between maternal glucose metabolism and childhood obesity.[86] The National Children's Study will measure glucose tolerance during pregnancy and will assess children's weight several times through age 21 to draw conclusions. A positive link could establish the need for increased emphasis on weight control before pregnancy—and for greater glucose control during pregnancy.

Does breastfeeding reduce the risk of obesity? Is the protective effect of breastfeeding due to breast milk itself, or to differences in feeding practices between breast and formula-fed infants? If breastfeeding helps to prevent subsequent obesity, it would be one of the few simple obesity-prevention measures available.[87] The National Children's Study can collect information about breastfeeding practices, obtain samples of breast milk, and assess body size multiple times during childhood and adolescence to answer this question.

How do diets low in fiber and whole grains, but high in refined sugars, increase risk for obesity and diabetes? Children's weights and measures of food intake can be assessed throughout the Study to answer this question. Because of the study size, the multiple subgroups of children, and varied diets, the Study has a unique opportunity to identify aspects of children's diets that contribute to weight control and could have a substantial impact on dietary recommendations.

Does the physical environment, such as sidewalks, proximity to parks, and a safe neighborhood, help prevent obesity? An improved understanding of the "built environment" that influences physical activity and overweight will assist planners in designing towns and neighborhoods that promote public health. In the National Children's Study, the characteristics of children's homes and environments will be assessed and physical activity levels will be determined through interviews, activity diaries, and measurements of children's body weights.

CHILD DEVELOPMENT AND MENTAL HEALTH

Perhaps the most prominent example of the environment's impact on child development involves lead exposure in children. Although the toxicity of high lead exposure had been known for many years, a series of reports in the 1970s began to link lead exposure to long-term learning and behavioral disabilities in children.[88] As the neuropsychological effects became evident at lower and lower levels of exposure, removal of lead from products including paint and gasoline has helped to significantly reduce the overall impact of lead on health. This example is indicative of the potential effect the Study results could have.

Exposures to toxic materials are known to affect a range of cognitive, sensory, and motor functions in children, as well as their social and emotional development.[89] Conditions believed to be affected by environmental factors include ADHD, autism spectrum disorders (ASDs), and mental retardation. The National Children's Study has a unique opportunity to gather information about these and other conditions to assess linkages with environmental influences.

Addressing Child Development and Mental Health

The Study will examine numerous research questions in the areas of child behavior, learning, neurodevelopment, mental health, and developmental disorders, including:

How does routine low-level pesticide exposure interact with genes to affect neurobehavioral and cognitive performance? The general adult population has had widespread exposure to pesticides, as reflected by urine tests conducted in previous studies.[90] Children often have greater exposure than adults due to increased contact with the ground and their tendency to put objects in their mouths. The Study can assess both *in utero* and postnatal exposures to pesticides with neuro-behavioral and cognitive examinations during infancy and childhood. Linkage to school records may also allow for the assessment of cognitive function.

Are early exposures to neurotoxicants—as lead and alcohol are known to be *in utero*—associated with developmental and mental health anomalies? Neurotoxicant exposure has been linked to increased aggression, delinquency, hyperactivity, impulsivity, poor socialization skills, and general difficulty with cognitive and intellectual activities.[91] The National Children's Study will monitor relationships between known neurotoxicant exposures and subsequent behavioral and cognitive changes, including interactions of exposures to multiple agents, as well as contributing elements that may be harmful as well as helpful to neurodevelopment, such as family dynamics, caregiver supervision, and classroom environments.

GENETICS

The ability to study gene-environment interactions is a new and pivotal opportunity to better understand the nature of health and disease in children. But knowledge of genetic susceptibility to diseases, particularly in relationship to environmental factors, remains in its infancy. Individuals vary in susceptibility, and it is now known that similar genes in different individuals—or even different groups—do not confer equal health risks. A critical aspect of gathering useful genetic data is the fact that environmental exposures occur at various stages of a child's life and can wax and wane in the same location. By combining genetic analysis with the assessment of environmental influences over time, the Study will bring genetic research to a new magnitude of utility and insight.

Addressing Genetics

The National Children's Study can employ the tools of molecular biology to investigate the role of genetic variation in disease, as well as disease-related vulnerabilities and predispositions in individuals and groups. The ability to assess these points across two decades and among 100,000 individuals at various ages presents a unique opportunity to generate new data and innovative health care strategies.

In what ways do environmental factors intersect with genes? National Children's Study investigators will use the latest knowledge about "target genes," suspected to be involved in the development of certain diseases, to develop broad-based conclusions about gene-environment interactions in large populations. The sequencing of the human genome has made this research possible by generating massive sets of data that allow scientists to study the links between genes and the environment.

With the completion of the human genome sequence in 2003, there is an extraordinary opportunity to analyze the interactions between genetic and environmental factors that affect health.

PHYSICAL ENVIRONMENT

The physical environment includes both the "built environment" and physical factors such as light, noise, and radiation. The built environment—the houses, stores, schools, playgrounds, and communities where children and families spend most of their time—is increasingly being recognized as a factor in health and illness. Highlighting the significance and complexity of built and physical environments in human health, a 2002 report published in the National Institute of Environmental Health Sciences' *Environmental Health Perspectives* describes vehicle pollution, particulate matter, poor housing conditions, crowding, and home and apartment pesticide use as only a few of the interrelating factors that contribute to child health problems.[92] Cause-and-effect relationships between physical environments and health, however, have been difficult to quantify and study in an orderly manner.

Addressing the Physical Environment

The National Children's Study can evaluate multiple aspects of built and physical environments through a variety of direct sampling and survey tools, including measurement of indoor exposures related to dust mites, cockroaches, mold, building materials, gas and wood-burning stoves, and pets. Potential research questions include:

Do aspects of the physical environment, such as housing quality and neighborhood and community conditions, affect child health and development? This question opens the door for evaluating relationships between inadequate housing, schools, and economically challenged communities and the presence of diseases, developmental disabilities, impacted school performance, and signs of chronic psychological stress. Inadequate housing is also often associated with the presence of airborne lead (or remaining lead paint), mold and mold toxins, and increased indoor pesticide use—all of which can be measured over time by National Children's Study investigators.[93]

Does household mold exposure in the first year of life lead to asthma? A recent study confirmed a strong association between the presence of mold in homes and apartments of newborns with the development of asthma.[94] (The same study noted a more modest, but still positive, association between cockroach infestation in homes of newborns and subsequent childhood asthma.) The National Children's Study can act on this compelling preliminary evidence by designing larger studies to investigate the relationships between built environments and allergens; toxins and the appearance of asthma; and other respiratory syndromes in children.

CHEMICAL ENVIRONMENT

Some 80,000 chemicals are in routine commercial use in the United States,[95] and a wide variety of these substances have been suspected to be toxic to developing brains and nervous systems. Lead, some solvents and glues, mercury and manganese, and some pesticides are demonstrated neurotoxicants that can pose serious harm to children as attention deficit disorders, nervous system aberrations, and memory, language, and intelligence impairments.[96] According to EPA's *2001 Toxics Release Inventory*, neurotoxicant chemicals—including persistent bioaccumulative toxins, which accumulate and remain in the environment and food chains—remain common elements of everyday American environments.[97] Although science has linked some chemicals to nervous system deficits, greater research is needed to monitor exposures and identify factors that may be tied to unexplained birth defects and developmental disabilities. Likewise, additional research may find that some chemicals are harmless, creating no cause for concern.

Addressing the Chemical Environment

The National Children's Study can monitor exposures to neurotoxicants, contributing vital data to information produced by birth registries and toxic chemical surveys and reporting systems. Critically important is the Study's ability to analyze genetic susceptibility to environmental "triggers" that may initiate gene-based nervous system damage. Some possible research questions include:

What happens to the human organism after long periods of low-dose exposure to chemicals, pesticides, and herbicides? The National Children's Study can assess chemical exposures over time through the sampling, tracking, and comparison of umbilical cord and infant and maternal blood samples. Longitudinal and comparative data can reflect variations in exposures across time and geographical locations. Other data-gathering techniques might include maternal questionnaires and software programs designed to rapidly detect significant correlations among regions, toxicants, and rates of disability.

What are the health effects associated with complex low-level exposures? Toxicants emitted into the environment at very low levels present a special challenge. These agents can be difficult to detect or to fully distinguish from other environmental factors. The National Children's Study can conduct sophisticated environmental and ambient air measurements and can analyze building materials. These data, coupled with surveys and questionnaires, will generate insight into causal associations between low-level exposures and diseases or conditions, if any, and help to establish threshold exposure levels as well as the interactive effects of combinations of exposures.

PSYCHOSOCIAL ENVIRONMENT

Despite progress in understanding the effects of psychosocial factors on the development of disease, more research on the links between social phenomena and physical illness or overall well being is needed. Family conflict, urban violence, economic stressors, parental occupational demands, and disparities in health care and public services all appear to play subtle roles in molecular and genetic processes, possibly initiating biologic pathways that predispose individuals to—or directly incite—physical illness. In the course of generating new data, the Study can uncover factors that enhance the psychosocial environment, while yielding a more reliable model of the health effects of psychological and social influences.

Addressing the Psychosocial Environment

Using surveys, medical histories, housing records, direct interviews, and sociological data, the National Children's Study can link psychosocial environments to clinical, genetic, and other information that may lead to improved strategies for intervention and care on many levels, including medical, public, and social services. Potential research questions may include:

How do social environmental factors contribute to diseases? Many studies have been published over the last decades suggesting that personal factors (e.g., school, family, relationships) can influence an array of physical symptoms and adverse behavioral and developmental changes. Most of these studies were limited by cohort size, period of time, or regions in which the research took place. Using various psychosocial measures in combination with clinical data, the National Children's Study can employ the advantages of a large participant population and greater time to help address this broad question.

Does chronic exposure to urban violence exacerbate asthma? Research completed in 2001 suggests that exposure to violence exacerbates asthma. In a small study of children in one inner-city neighborhood, there was a temporal association between exposure to violence and flares of asthma symptoms (e.g., wheezing, coughing).[98] The National Children's Study might further this investigation on a much broader scale by merging data on the incidence of violent episodes with patterns of asthma, based on family diaries and hospital and clinic measures.

How do differences in the social environment across many complex factors produce health disparities between urban and rural residing children? Lifestyle, occupation, and behavioral patterns vary among children living in cities versus rural areas. The National Children's Study can examine the role these factors might play in the health and disease outcomes those groups experience.

BIOLOGIC ENVIRONMENT

Research has confirmed that exposure to certain toxicants can create marked immune system dysfunction, which increases an individual's susceptibility to viruses, bacteria, and fungi.[99] This relationship between immunity, infection, and the environment has profound implications for the health of children. But scientists do not know the full extent or severity of immune system deficits related to environmental factors. Some believe that a child's immune system can withstand the pressures of environmental insults; others believe that developing immune systems are at serious risk when exposed to toxicants. Additionally, some researchers have noted that, because children are not "little adults," questions remain about the long-term implications of immune damage sustained early in life. The debate goes to the heart of a significant area of research for the National Children's Study.

Addressing the Biologic Environment

The National Children's Study can evaluate the biologic environment by intersecting data culled from medical records (e.g., incidence of infectious diseases among participants at different ages and in specific locations), as well as from on-site sampling of ambient air that is tested for the presence of bio-allergens. Other assessments can include vector sampling (e.g., shared surfaces in homes and public areas), blood cultures and throat swabs for microbiologic assessment, and inflammatory biomarkers (e.g., erythrocyte sedimentation rate, C-reactive protein levels).

Do chemical toxicants consistently suppress immunity and facilitate infections? The National Children's Study can measure environmental toxicant levels in specific locations and compare that data against the incidence of a variety of infectious diseases, including immune-mediated entities such as asthma, hypersensitivity reactions, and chronic dermatitis. The Study can also use genetic methods to monitor immune system and inflammatory changes at the molecular level, in concert with known chemical exposures.

Do specific infections incite heart disease? The role of inflammation in heart disease is well-established in adults, but a growing volume of data supports the possibility that infections early in life may also play a role. The National Children's Study can investigate the linkages between specific common pathogens and evidence of heart and vascular disease early in life. It also can track individuals across time to assess the progression of disease, from the earliest molecular changes to more overt signs and symptoms. Along the way, data on diet and exercise regimens could provide additional information about the ways in which heart disease is initiated and ameliorated.

Does prenatal infection and inflammation increase risk of cerebral palsy and autism spectrum disorders? Previous studies have shown that exposure to prenatal infection or inflammation may increase risk of cerebral palsy.[100] Less data are available on a possible link to ASDs. The Study can assess prenatal infection and inflammation through the pathologic and microbiologic evaluation of placentas. Assessment of the neurodevelopment of children can include diagnostic algorithms that identify all cases of cerebral palsy and ASDs. A review of medical and school records may also help identify cases of these disorders.

What factors during pregnancy are associated with increased risk of schizophrenia? Because it is known that schizophrenia is related to genetic predisposition in only half of all cases, the Study is well-positioned to investigate other causes. Prenatal exposure to infectious agents, such as herpes simplex type 2 (genital herpes), has long been thought to have a link to the development of schizophrenia. The National Children's Study will consider the timing of infection in relation to birth by collecting multiple blood samples during pregnancy. If exposure to certain infections is associated with schizophrenia, better understanding, detection, and management of the disorder will be possible.

GROWING AND LEARNING: A CHILD'S DEVELOPMENT

Milestones in a Child's Life

BIRTH DAY: THE BEGINNING

Weighing 25 percent of its eventual adult weight, the brain of a newborn is still developing the synapses and neurons that enable the senses and memory.

YEAR 1: TAKING STEPS

Around his first birthday, he is taking his first steps. A great adventure for the child, walking is a motor skill that requires coordination, balance, and practice.

YEAR 3: WHO AM I?

Although still a toddler, a three-year-old is developing a healthy sense of self-esteem and a sense of empathy for others. The critical development of the brain continues as her vocabulary grows and curiosity develops.

YEAR 5: YOUNG AND GIFTED

She ties her own shoelaces, writes her own name, knows right from left, and relies on her 10,000-word vocabulary. Around the age of five, she has developed a hand preference and is seeking knowledge from her environment.

YEAR 7: MOVING OUT

Throwing, jumping, catching, batting, and other large-muscle motor skills are improved between the ages of seven and eight. Both boys and girls often start to join organized games and activities such as soccer, basketball, or dance.

YEAR 10: HUMOR ME

Laugh and a child laughs with you. By the age of 10, a child can understand humor, metaphors, and wit. Also, he can switch the flow of a conversation to match another person's needs or moods.

BIRTH

After months of preparation and anticipation, the child is welcomed into the world. He joins his parents as participants in the National Children's Study and important data are collected about him.

AGE 1

The first results from the National Children's Study are available and will provide insight on some outcomes related to events during pregnancy (e.g., maternal nutrition during pregnancy and prenatal care). During this stage of development, researchers can check an infant's respiratory and immune systems to detect early markers of asthma.

AGE 3

The toddler is developing communication skills and exploring the environment around him. The early clues as to the development of autism can be detected by this age (if not earlier).

AGE 5

The school environment brings new opportunities for intellectual and social development. The researchers and scientists of the National Children's Study can measure ability to learn and check for learning disabilities.

AGE 7

The child is able to understand his or her special involvement in the National Children's Study.

YEAR 11: CHANGES

The first phases of puberty have occurred for many children by ages 11 and 12. Growth spurts, voice changes, hair growth, and mood changes mark these hormonal changes.

YEAR 14: FITTING IN

After adjusting to the new social setting of high school, he may be concerned with appearance and gaining the approval of friends and classmates.

YEAR 15: STRETCHING MY WINGS

She has become more autonomous, planning her daily activities and taking more responsibility for her life. By age 15, she has developed a sense of responsibility and a sense of identity.

YEAR 17: INDEPENDENCE

No longer a baby but not yet an adult, he takes the great leap into financial, social, and personal independence. Whether off to work or college, he is preparing for adulthood.

YEAR 21: ALL GROWN UP

The baby who once crawled and climbed over the furniture has now reached physical maturity. Her brain, now weighing three pounds, is fully developed, and all gross and fine motor skills have matured. Despite physical maturity, there is more growth to come in adulthood, which brings its own developmental milestones and challenges.

AGE 10

How the child interacts with peers in social and educational settings will tell researchers something about his social development thus far.

AGE 13

The child's environment can enhance or impede her physical development. Researchers will know if puberty is on track and how diet, exercise, and the built environment are affecting growth.

AGE 16

The National Children's Study research team can see evidence of the teen's support systems and capabilities to make good personal choices.

AGE 21

The young adult has graduated from high school and has begun to establish a new life for herself, independent from her parents. She is making decisions that impact her education, career, personal life, and well being.

A Child's Development as a Study Participant

MOVING FORWARD: MEETING THE CHALLENGES OF THE NATIONAL CHILDREN'S STUDY

Laying the Groundwork: Pilot Studies and Discussion Groups

The research questions reflect the ambitious scope of the National Children's Study. Its research plan has tremendous range and significance. Study designers are fully aware of the extent of the challenge and the dimensions of the work to come.

The National Children's Study has already initiated a number of preliminary research efforts that will allow investigators to understand where challenges lie and what obstacles might be encountered. Already producing useful data, these efforts ensure that the Study identifies the best and most cost-efficient methods and practices for meeting complex scientific goals.

For more than three years, scientists from many disciplines, including medicine, environmental science, chemistry, biostatistics, social and behavioral sciences, and human growth and development, have worked to build a foundation for the National Children's Study. These efforts, collectively known as "pilot studies," range from evaluating the possibility of recruiting primary care physicians as local Study researchers, to finding inexpensive and unobtrusive techniques for measuring various exposures in homes and schools, to identifying the best ways for collecting and storing specimens, to ensuring accuracy in the data from numerous Study sites within the United States.

These pilot studies, which will be conducted throughout the life of the Study as new issues and challenges arise, encompass the questions that must be addressed to enable a functional and cost-effective National Children's Study. As results from the pilot studies become available, they will be incorporated into the research design.

Among the pilot efforts are *exposure studies*, which seek to predict the where, when, and why of environmental exposures, along with the different pathways of those exposures. For example, because infants interact with their environment differently than older children and adults, it is essential to understand what exposures they encounter and how these exposures can be accurately measured.

Health-related studies evaluate and recommend testing and measurement techniques. Efforts are under way to develop simple, reliable, and inexpensive "field-ready tests" to assess and measure child development.

Study design pilot studies explore different ways to conduct a study, such as optimal approaches to involving communities and recruiting participants.

Cross-cutting studies combine the insights of scientists working in different disciplines. A geneticist may partner with an environmental chemist, a pediatrician, and an ethicist, for example, in an effort to identify the ways in which genes interact with a specific chemical exposure to influence child behavior in different locations in the United States. Cross-cutting studies capitalize on multidisciplinary collaborations in many of the Study theme areas simultaneously, and, along the way, offer exceptional potential to identify new and emerging technologies of use to the National Children's Study. Such studies also lay the groundwork for a children's environmental health research database of substantial utility and range.

This is a once-in-a-lifetime opportunity. It will shape the research agenda for the next generation.

Robert Chapin, Ph.D., head, Investigative Developmental Toxicology Lab, Pfizer Pharmaceuticals

In the context of these strategies and techniques, experts from various disciplines relevant to the Study have assembled as working groups to discuss the scientific, medical, and ethical issues pertinent to a study of this magnitude. Numerous analytical papers have been or are now being prepared, looking at the "state of the art" in the interconnecting scientific arenas that comprise the Study's research themes.

Administrators and investigators remain aware that, as the Study unfolds, new challenges will arise. Participants will age, society will evolve, new technologies will emerge, and scientific and health priorities will respond to shifting needs and capacities. The National Children's Study pilot studies are preparing for the road ahead, laying critical groundwork to ensure that the Study reaches its goals and offers a substantive return on investment in terms of health, knowledge, and new capabilities.

Planned Approaches to Study Challenges

CHILDREN AS RESEARCH PARTICIPANTS

It has become increasingly clear over the last 30 years that toxic exposures have different—and sometimes more serious—effects on children than adults. For a long time, children were excluded from clinical research because the risks were considered too great. But now the nation realizes that not including children in research poses even greater risks to public health and safety. If children are at the highest risk, they need and deserve our best research efforts.

The National Children's Study is a response to the need for new knowledge in the area of environmental exposures in children. But what are the issues surrounding recruitment of children before birth, long before they can express an opinion about their participation?

There are established precedents for the safe and responsible recruitment of children, and institutional regulations govern ethical conduct of research involving children. National Children's Study planners are committed to making every effort to ensure participants' safety.

The recruitment of children is generally achieved with at least one parent's or guardian's permission. As part of this informed consent process, the National Children's Study will discuss important aspects of the Study's structure, intent, and methods with every mother, father, or guardian involved.

The Study will adopt a policy of open communication that emphasizes clarity and accessibility. Informational materials, Web sites, informed consent forms, and possibly interactive consent computer programs will be made available at appropriate reading levels and in the languages spoken by the families involved.

The families of participating children (and, eventually, the children themselves) are the pivotal Study partners. They will be encouraged to provide ongoing feedback on their experiences in the Study. Their questions, problems, and issues will be critical to creating the balance that will guide the conduct of the National Children's Study, ensure responsible and responsive Study management, and make this a truly unprecedented national research effort.

PARTICIPANT CONFIDENTIALITY

In discussion groups conducted during the Study's planning stage, expectant and current parents and other stakeholders consistently raised privacy as a key issue. Community leaders and health care providers echoed these concerns. All believe that participants must clearly understand the Study's benefits, promise, and process for protecting the privacy of personal data.

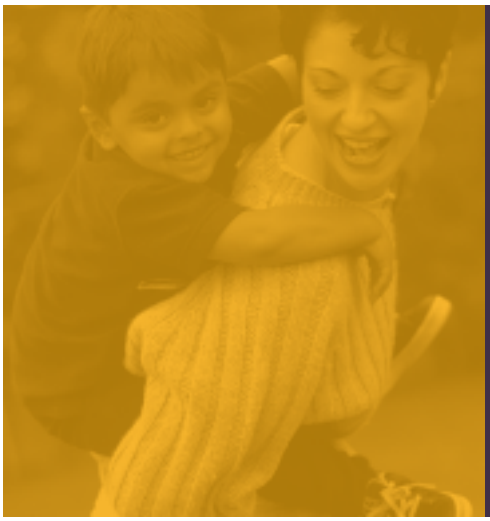
Prospective participants may wonder about the ability of any large-scale study to protect their family's private information over the long term. They might fear that employers, health insurers, and other third parties will gain access to their information. To address these concerns, the National Children's Study will devote careful attention to personal privacy. Among other protections, DHHS recently released new guidelines under the Health Insurance Portability and Accountability Act of 1996 to protect the confidentiality of individuals' medical records, which the National Children's Study program staff will follow. Study coordinators will also construct the Study's databases to ensure the protection of privacy (e.g., encrypted sites and secure data entry forms) and will proactively address security issues (e.g., protecting data from outside attack).

The National Children's Study also will rely on institutional review boards to review ethics safeguards and participant protections. The Study may assemble an independent panel to provide an extra level of review in managing issues related to confidentiality.

PROTECTING PARTICIPANTS (INFORMED CONSENT)

A critical factor in mounting such a broad-based research effort hinges on how individuals will give

The National Children's Study is a national response to the need for new knowledge in the area of environmental exposures. If children are our most at-risk population in this arena, they need and deserve our best research efforts.



Every American citizen is a stakeholder in the nation's future, and, as such, shares the rights and responsibilities inherent in well-informed decision making. Informed consent affirms and actualizes the national commitment that scientific research must never take precedence over the safety and well being of individuals participating in that research.

permission for their children's participation in the National Children's Study.

Informed consent is the mechanism by which any individual choosing to participate in research does so independently and on the basis of open communication about a study's aims, goals, and potential risks and benefits. Informed consent also provides a potential participant with adequate time to reflect before making a decision. It is fully embraced by the National Children's Study and supported by rigorous federal guidelines for investigators and individuals that govern the ethical conduct of research, especially efforts involving pregnant women and children.

Within this context, the following series of related concepts drive the Study's approach to informed consent:

- Informed consent is fundamental to the Study.
- The risk posed by participation in the Study is expected to be minimal.
- Additional safeguards will be in place to protect the rights and interests of child participants.
- Because participants will reflect the diverse nature of the United States, every effort will be made to provide useful Study information in understandable terms and appropriate languages.
- When Study participants reach a predetermined age, they will have the opportunity to actively affirm their parents' endorsement of their participation in the Study.

PARTICIPANT RECRUITMENT

Recruiting and retaining 100,000 participants is unquestionably the greatest challenge for the National Children's Study. Because the Study will begin by following fetal health, Study coordinators must enroll pregnant women early enough to monitor their fetuses as well as their diets and other factors. Enrolling such a large number of participants—from every corner of the country and virtually every racial, ethnic, and socioeconomic group—will require a coordinated effort of research staff, health care providers, and intermediaries who can reach and inform families about the Study. Recruitment is slated to begin around 2006, after the National Children's Study is launched, and will last through 2011.

Study information materials must emphasize benefits while allaying potential concerns. Study coordinators are designing a strategy that meets these needs,

including a major information campaign that will educate the public about the Study and promote recruitment. The campaign will commence at the Study launch and will run at least through the recruitment phase. In addition, recruitment teams will carry out local campaigns within communities hosting the Study. Every participating clinic and hospital will also receive assistance with setting recruitment goals and providing information for the population(s) they serve.

Study planners anticipate that intense, local grassroots campaigns will yield the greatest recruitment for each site. Local campaigns will promote the formation of community partnerships; build relationships with area obstetricians and other health care providers; and direct outreach to parenting groups, religious and community institutions, and other organizations offering health information and support to families. Previous studies have demonstrated that endorsement and referral from trusted community leaders is a significant factor in encouraging study participation.

PARTICIPANT RETENTION

The task of keeping track of 100,000 families, through changes in family structure, new residences, and departures for college or work, is formidable. The National Children's Study is developing a retention strategy that builds on its recruitment efforts and draws from past study successes. Because it is such a crucial aspect of the Study, retention is being considered at virtually every step of the planning process, from protocol design and ethical considerations to data monitoring and recruitment. Study planners will not take for granted anything that might compromise a family's ability or willingness to stay the course of the Study.

Building trusting relationships with community leaders will be critical to the success of the recruitment efforts.

According to published reports on previous longitudinal studies, a critical factor in keeping participants "on board" is the bond they develop with Study staff and fellow participants. That Study investigators and support staff, in particular, personally care about the children and families involved is a powerful motivator toward continued participation. Building on the relationships between participants and Study staff, the National Children's Study will seek to create a community of "National Children's Study Families" in which each site—as well as the entire community—recognizes and celebrates the role of participants. Some tools and activities to promote connection and cohesion among participants may include newsletters (both electronic and print), interactive Web sites for the children, periodic get-togethers, public presentations, and birthday greetings. As in most studies of this kind, participants will receive incentives for their continued participation.

Study coordinators will need to be creative and flexible in developing ways to keep 100,000 families engaged in the Study through its completion.

COMMUNITIES OF THE NATIONAL CHILDREN'S STUDY

NATIONAL CHILDREN'S STUDY SPONSORS

- U.S. Department of Health and Human Services
  - — National Institutes of Health
  - — Centers for Disease Control and Prevention
- U.S. Environmental Protection Agency

EXPRESSING THE VISION FOR THE NATIONAL CHILDREN'S STUDY

The Health and Economic Benefits of the National Children's Study

America faces critical health issues on many fronts. Across an array of disorders and diseases, often seen first in children and affecting their lives into adulthood, the nation's scientists, physicians, parents, policy makers, and concerned citizens are supporting a call to action: more research, better research, reliable outcomes, and substantive results.

The health and medical burdens we face are complex and widespread. We know, for example, that children bear an increased vulnerability to various types of exposures; that they are not simply "small adults"; and that they do not have the same immune protection or detoxification capacities as adults. And, because they are children, they have little or no ability to protect themselves in abuse or neglect situations.

The urgency and significance of the challenges to child health are clear, but there are scientific barriers to address. Much of the evidence to date establishes links between specific exposures and specific outcomes. And even though many of these relationships are undeniable, considerable work remains to understand the subtle molecular and genetic mechanisms involved.

The lessons of the Framingham Heart Study, the Bogalusa Heart Study, and the Nurse's Health Study, among others, demonstrate the benefits of broad-based, long-term multiple-question health studies. The health and economic benefits of the National Children's Study—realized through reduced illness and disability, as well as through increased school and work productivity—will profit the nation well beyond the investment of creating and maintaining the Study.

With its emphasis on multiple environmental exposures and health outcomes across more than two decades, the National Children's Study will combine scientific efficiency with cost-effectiveness. Evaluating data exposures in relation to genetic predispositions to health and disease among 100,000 participating children will help create a more complete picture of what actually causes diseases and promotes health. Although it cannot promise to prevent or treat every child health problem, the National Children's Study will provide a data repository from which new preventions and treatments can be developed for some of today's most common health disorders.

I am convinced that this study, if successful, will be remembered for years to come as one of the most important scientific enterprises ever started regarding children's health.

Fernando Martinez, M.D., professor, Pediatrics, University of Arizona

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