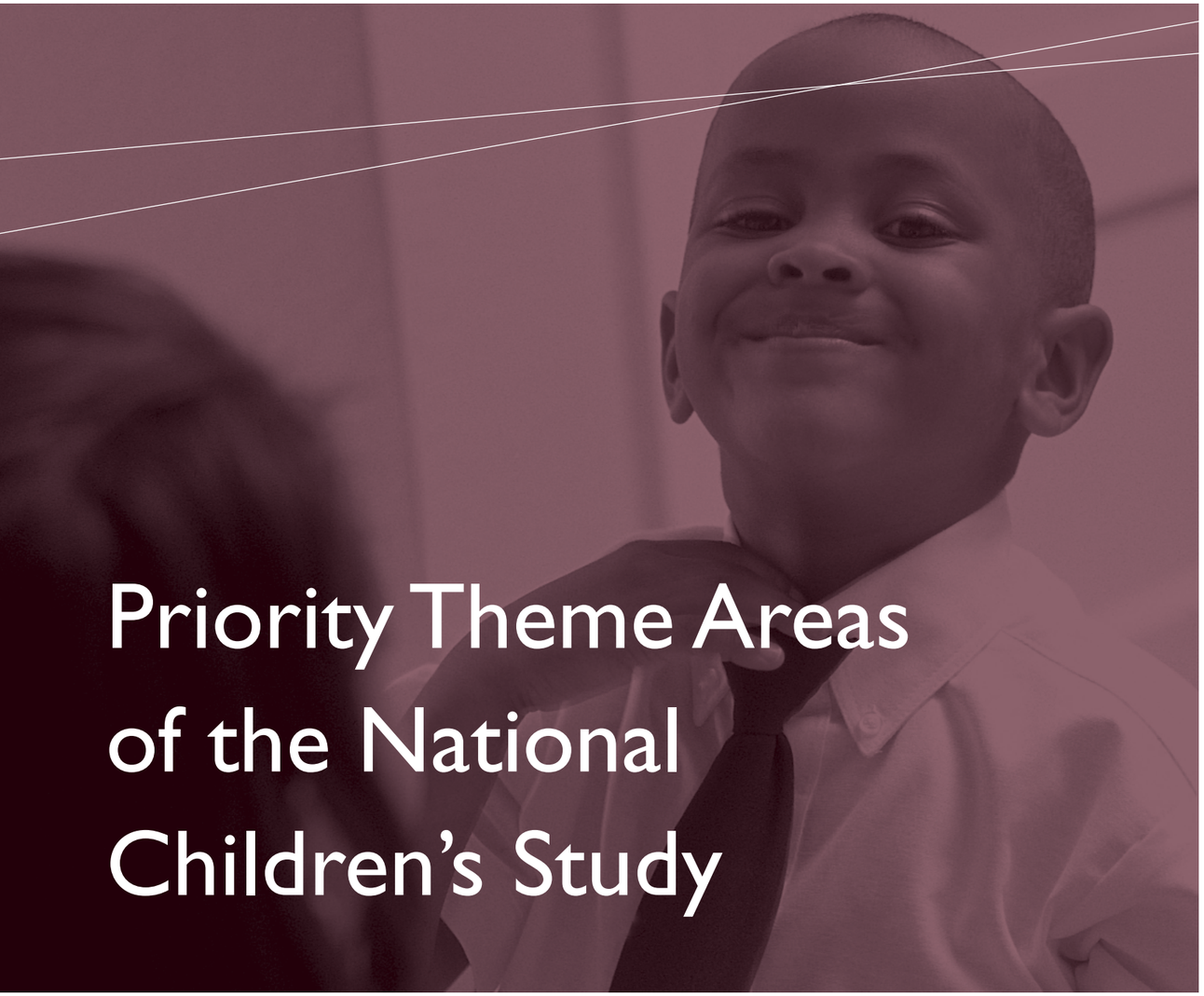

Priority Theme Areas of the National Children's Study

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.

BUILDING THE NATIONAL CHILDREN'S STUDY

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.