PART I: BACKGROUND AND SIGNIFICANCE

1. BACKGROUND

Patterns of illness among children in the United States and other industrially developed nations have changed substantially during the past 100 years (Bloom & Dey, 2004). Before and during the first half of the last century, infectious disease comprised the principal threat to children. In contrast, the major illnesses and disorders that impair health, growth, and development today are chronic conditions stemming from the complex interaction of environmental exposures and inherent genetic factors. Some label this the "new pediatric morbidity" (Haggerty, 1975). These conditions include: premature births (Ananth, Joseph, Demisse, & Vintzileos, 2005); asthma (Mannino et al., 2002); injuries (Thornton, Craft, Dahlberg, Lynch, & Baer, 2002); childhood cancer (Linet, Ries, Smith, Tarone, & Devesa, 1999); neurodevelopmental disorders, such as learning disabilities, dyslexia, mental retardation, attention deficit/hyperactivity disorder, and autism (Boyle, Decoufle, & Yeargin-Allsopp, 1994; Newschaffer, Falb, & Gurney, 2005; Scahill & Schwab-Stone, 2000; Shaywitz, 1998); obesity and type 2 diabetes (SEARCH Writing Group, 2004); birth defects such as hypospadias (Paulozzi, 1999); and cardiac defects (Towbin et al., 2006). Addressing the causes and contributors to these and similar chronic conditions is the major challenge to public health practitioners and pediatric researchers today, and constitutes the frontier that must be crossed if the health and well-being of children in developed countries is to move forward. The National Children's Study is designed to address these issues with robust science and the ability to generalize the data to the U.S. population.

The National Children's Study's design rests on the principle that both health and susceptibility to disease are determined by dynamic processes that occur throughout life. Perturbations ("insults") that impact health states may occur any time from preconception through adult life. These insults can affect viability, differentiation of major organ systems, somatic growth, and the development of functional processes including maturation of metabolic systems. A range of determinants acting either in concert or synergistically may impact growth and development. These include the built and natural environments with their chemical and physical factors, the social environment, individual behaviors, and biological factors including genetics. Of particular importance are the earliest stages of human development, pregnancy and early childhood, when cell division, differentiation, and maturation are most rapid.

These health determinants may influence development in many ways. For those with high potency when acting at critical periods of development, such as thalidomide or Accutane, severe birth defects will result in most exposed offspring. Most environmental factors, however, are not so potent. More often, factors operating at critical or sensitive periods of development will interact with other factors over the life course to raise or lower the risk of adverse health outcomes. These factors may be genetic or non-genetic. For example, accelerated weight gain during childhood is associated with increased risks of diabetes and cardiovascular outcomes later in life; this phenomenon is accentuated among children born with restricted fetal growth (Barker, 2005; Bhargava et al., 2004). The risk of orofacial clefts due to maternal cigarette smoking is markedly increased in children with certain genetic traits and/or reduced folic acid intake (Lammer, Shaw, Iovannisci, & Finnell, 2005; Shaw et al., 2005; Shaw, Wasserman, Murray, & Lammer, 1998). Only with this appreciation of the complexity of interactions among genetic and environmental factors will we be able to inform the next generation of caregivers about effective prevention and treatment to lower the burden of common chronic conditions of childhood and later-onset diseases that arise from early developmental insults.

1.1 The Children's Health Act of 2000

Faced with the challenge of how to address the potential risks of many environmental factors that may be affecting the health and development of children, the President's Task Force on Health Risks and Safety Risks to Children concluded in 1999 that a large study to define the actual risks associated with broad environmental exposures is an essential first step. Following the recommendation of the task force, the U.S. Congress passed the Children's Health Act of 2000, which directed the National Institute of Child Health and Human Development (NICHD) to conduct a national longitudinal study of environmental influences on children's health and development. The National Institute of Environmental Health Sciences (NIEHS), the Centers for Disease Control and Prevention (CDC), and the U.S. Environmental Protection Agency (EPA) joined the NICHD in planning this study.

The Children's Health Act of 2000 (Public Law 106-310 Sec. 1004) specified that the study should extend from the prenatal period to adulthood, following a sample of children across development. It should investigate the short-term and long-term influences of physical, chemical, biological, and psychosocial environmental exposures on children's health and development, including not only physical health, but behavioral, emotional, and educational outcomes as well. The study should elucidate both those factors that protect children from detrimental outcomes and those that put them at risk, including sufficient diversity to address the existence and consequences of health disparities among children in the United States. The scientific rationale for this program of research, now named the National Children's Study, is described below.

1.2 Rationale for the National Children's Study

1.2.1 The Public Health Burden of Childhood Chronic Conditions

While there are many important conditions of childhood that have grave effects on certain individuals and families, there are some that also place a great burden on the population because of their prevalence, severity, and/or cost. For example, there are increasing concerns about the large (and perhaps growing) number of American children who have one or more major chronic health or developmental conditions. As many as 17 percent of children have some type of developmental disorder (Boyle et al., 1994), about 21 percent have a diagnosable mental or addictive disorder with at least minimum impairment (U.S. Department of Health and Human Services, 2000), and about 7 percent have asthma (Mannino et al., 1998). The NCS is particularly poised to examine these conditions because it is a large study of the general population. Through the extensive planning process of the NCS, the following areas emerged as primary outcomes around which the Study's core hypotheses have been generated: pregnancy outcomes; neurodevelopment and behavior; asthma; obesity and growth; injury; and reproductive development. Additionally, the NCS is committed to assessing predictors of healthy development. The data collection process will also allow the examination of a range of health outcomes that extend beyond those identified in this Study.

The priority outcome areas were chosen not only because of their importance to public health, but also because a research study of the scope and magnitude of the NCS is required to understand their origins and course. Since many of the outcomes may arise as a consequence of in utero exposures, study of these outcomes must begin before birth. Additionally, a variety of exposures likely contribute directly, indirectly, and interactively to these outcomes. A full understanding of their etiology requires a study covering a range of exposures. Genetics could also play a role both in the origin and expression of disorders, thus a complete study must include an exploration of direct genetic contributions and of gene-environment interactions. Furthermore, each outcome has a meaningful range of manifestations over the course of development, including sensitive periods for exposures, different ages of onset, and changes in

nature or severity over development. Only a longitudinal study can track these outcomes as they unfold during childhood and adolescence. Finally, to examine these exposure-outcome relations in a definitive manner, the Study must have sufficient power, and thus sufficient sample size, to explore both normative and low-prevalence outcomes. The NCS will follow a representative sample of 100,000 children from before birth to age 21 and will include assessments, collected through a variety of modalities, of chemical, physical, psychosocial, and biological exposures, as well as genetics. Incorporating both breadth and depth of investigation, the NCS will be particularly well suited to provide scientists and practitioners with the tools to address these new childhood morbidities, and to promote health and well-being in our children.

1.2.1.1 Pregnancy Outcomes

Low birth weight and preterm delivery are highly correlated and continue to be among the major refractory causes of infant mortality and childhood morbidity (Gutbrod, Wolke, Soehne, Ohrt, & Rigel, 2000). Identified environmental factors for increased risk of preterm birth, which include maternal smoking (Kyrklund-Blomberg, Granath, & Cnattingius, 2005), chemical agents (Gonzales-Cossio et al., 1997; Hinckley, Bachand, & Reif, 2005), infection (Andrews, Hauth, & Goldenberg, 2000; Pararas, Skevaki, & Kafetzis, 2006; Romero, Espinoza, Chaiworapongsa, & Kalache, 2002), stress (Hobel, 2004; Park, Park, Lockwood, & Norwitz, 2005), and even air pollution (Rogers & Dunlop, 2006), all point to environmental exposure etiologies. More recent reports point to more complex interactions between environmental and genetic factors. Several possible genetic variations have been described that place some women at particular risk of premature births with certain exposures, such as infection (Varner & Esplin, 2005) and cigarette smoke (Wang et al, 2002).

Birth defects are the leading cause of infant mortality and are responsible for more than 8,000 (approximately 20 percent) of the 40,000 infant deaths that occur annually (CDC, 1998). Following on the morphologic birth defects of fetal exposure to alcohol (Jones, Smith, Ulleland, & Streissguth, 1973), there are concerns about other birth defects such as hypospadias that have increased in recent years along with exposures to phthalates and other endocrine active compounds (Paulozzi, 1999; Rogan, Gladen, Guo, & Hsu, 1999; Weiss, 2002). There are also concerns about central nervous system defects, such as anencephaly, spina bifida, and hydrocephaly, and their association with diabetes, with lesser alterations possibly associated with altered glucose metabolism (Anderson et al., 2005).

1.2.1.2 Neurodevelopment and Behavior

In contrast to birth defects which are structural in nature, developmental disabilities are recognized because of abnormalities in functioning that emerge as a child ages. Almost 20 percent of all children in the United States are reported to have some type of developmental disability (Boyle et al., 1994), including approximately 2 percent of school-age children with a serious developmental disability (Crain, 2000). Conditions that are representative of developmental disabilities include mental retardation, cerebral palsy, attention deficit/hyperactivity disorder (ADHD) and autism. Numerous exposures in utero and during infancy, most notably lead (Lidsky & Schneider, 2003), alcohol (Mattson & Riley, 1998), and nurturing (Bradley et al., 1989), have been identified as affecting neurological and cognitive development. The causes of most cases of mental retardation, however, are unknown (Yeargin-Allsopp, Murphy, Cordero, Decoufle, & Hollowell, 1997). Recent evidence reveals the potential contribution of known neurodevelopmental toxicants to developmental disabilities at levels of exposure well below currently recognized levels of toxicity (Lanphear, Vorhees, & Bellinger, 2005; Schober et al., 2003). Previously unidentified environmental agents, including persistent and nonpersistent pesticides as neurotoxicants, may also play a role in developmental disabilities (Kofman, Berger, Massarawa,

Friedman, & Jaffar, 2006; Rice & Barone, 2000; Weiss, 2000). The cost of diminished child functioning due to environmental toxicants is substantial (Grosse, Matte, Schwartz, & Jackson, 2002; Salkever, 1995; Weiss, 2000).

The etiology of neurodevelopmental disorders can be complex and difficult to specify. For example autism is a neurodevelopmental disorder that was once believed to be rare (i.e., 4-5 per 10,000 children); however, the number of individuals receiving services for autism has increased dramatically in the past 10 years. The current prevalence of autism and the broader group of autism spectrum disorders stands at about 3-6 per 1,000 children (Gillberg & Wing 1999; Hirtz, 2000; Rutter, 2005; Yeargin-Allsop et al., 2003). Although autism has a strong genetic component (The Challenges of Autism, 2000), environmental and social factors are also thought to play a significant role in its expression, and a number of environmental agents have been suspected of interacting with genetic factors to cause the apparent increase of autism.

1.2.1.3 Child Health and Development

In addition to investigation of specific disorders of childhood, an understanding of child health and development involves examination of individual differences and children's trajectories through time on measures of health, well-being, social and emotional development, and cognitive development and achievement.

Early developmental deficits can compromise subsequent social and academic success. While most children enter kindergarten having mastered basic skills, a significant percentage lags behind in key domains. Between 18 to 42 percent of preschoolers are estimated to lag behind their classmates significantly in their preparedness for learning (West, Denton, & Germino-Hausken, 2000). In the realm of behavior and conduct, approximately 12 percent of infants and toddlers have significant behavioral or emotional problems (Briggs-Gowan, Carter, Skuban, & Horwitz, 2001). Such problems unfold in complex ways over time, however, as research indicates that less than 50 percent of children with conduct problems during the toddler or preschool period continue to have significant problems one to two years later (Baillargeon et al., 2007; Lavigne et al., 1998). Additionally, children who show early signs of social competence tend to become even more prosocial with development (Baillargeon et al., 2007). Nonetheless, many children with deficits in emotional, social, and cognitive skills at school entry are likely to have both ongoing conduct problems, and difficulties with academic achievement (Wentzel & Asher, 1995).

Many different experiences and exposures have the potential both to affect child health and development at sensitive periods and to change children's developmental trajectories. For example, sensitive parenting and secure infant-parent attachment during infancy predict children's subsequent competence and healthy social functioning (Thompson, 1999). In contrast, parental mental health problems can lead to disturbances in parent-child interactions (Jameson, Gelfand, & Kulcsar, 1997), and the strategies that a young child uses to relate to a mentally distressed parent can become persistent, resistant to change, and can develop into a long-term behavioral pattern of response (Field, 1995; Lyons-Ruth, Wolfe, Lyubchik, & Steingard, 2002). Contexts outside the family can also have great impact on children. Early experience in high-quality center-based child care predicts better vocabulary skills, but also slightly elevated aggressive behavior in middle childhood (Belsky et al., 2007). The sensitive periods for exposure and trajectories of functioning are multifaceted and are also likely moderated by genetic and physiological factors (Curtis & Cicchetti, 2003). Longitudinal research with a sufficiently large and representative sample is needed to untangle these intricate pathways.

1.2.1.4 Asthma

Among children, asthma is the most common chronic illness (National Academy of Sciences, Institute of Medicine, 2000). Asthma prevalence in the United States, estimated from the National Health Interview Survey (NHIS) by the American Lung Association (American Lung Association Epidemiology and Statistics Unit, 2006), shows the prevalence of asthma increased 85 percent from 1982 through 1996 to an estimated 14.6 million persons (55.2 per 1,000). This increase was 76 percent in children younger than 18, or 4.43 million persons in 1996 (62.0 per 1,000). This trend paralleled increasing asthma hospitalization and death rates in children (Akinbami, 2006; American Lung Association Epidemiology and Statistics Unit, 2006). In 2004, the prevalence of doctor-diagnosed asthma reached 30.2 million Americans (104.7 per 1,000), including 6.5 million children younger than 18. Almost 4 million children younger than 18 were estimated to have experienced an asthma attack in 2004. Prevalence data in the United States, both from the 12-month prevalence (before 1997) and 12-month attack prevalence of asthma (since 1997), were highest among children ages 5-14, higher among Blacks compared with whites, and higher among females than males (Akinbami, 2006; American Lung Association Epidemiology and Statistics Unit, 2006). Approximately 38 percent of the hospital discharges related to asthma in 2004 were in children younger than 15, although only 21 percent of the U.S. population was younger than 15.

Asthma is associated with substantial physical and behavioral disability among children. Thirty percent of children with asthma reported activity limitation compared to 5 percent of children without asthma, and asthma was estimated to account for 10 million missed school days and 13 million physician contacts among children in 1988 (Taylor & Newacheck, 1992). This is an underestimate of the current burden because of increasing trends in asthma prevalence and associated morbidity (Mannino et al., 2002). The annual estimated cost of pediatric asthma in the United States in 1997 was $6.6 billion (Landrigan, Schechter, Lipton, Fahs, & Schwartz, 2002).

In 2004, the total cost of asthma was estimated at $16.1 billion, including $11.5 billion in direct health care costs and $4.6 billion in indirect costs (lost productivity) (National Institutes of Health, 2004). The severe forms of asthma account for a disproportionate amount of the direct costs. Malone, Lawson and Smith (2000) estimated that less than 20 percent of asthmatics account for more than 80 percent of the direct costs. Asthma also poses a substantial and increasing public health burden because of school absences and restriction of children's usual physical and social activities (Newacheck & Halfon, 2000).

Asthma is a complex disease characterized by pulmonary obstruction due to inflammatory response within central and peripheral airways. Asthma has a variety of clinical phenotypes, which carry implications for disease etiology, evolution, and severity (Martinez, 2000; Martinez & Helms, 1998). Current understanding of the etiology and severity of asthma focuses on individual response to a range of interacting immunogenic and immuno-protective factors (Busse & Lemanske, 2001): air pollution and bioaerosols (including allergens, endotoxin, and mold); respiratory tract infections; maternal stress; dietary antioxidants; and early exposure to bacterial and microbial products. This focus opens a range of potential research areas that address interactions between host response (e.g., individual inflammatory response, genetic makeup), potential inflammatory triggers (e.g., ozone, particulate matter, and other airborne pollutants; viral infection; animal or fungal antigens), and potential protective factors (e.g., early exposure to bacterial endotoxin, dietary antioxidants).

1.2.1.5 Obesity and Growth

The prevalence of overweight among children is greater than 15 percent among children age 6 or older, and this prevalence has increased during the past 40 years (Ogden, Flegal, Carroll, & Johnson, 2002). Being overweight as a child is a risk factor for being overweight as an adult (Serdula et al., 1993) and is associated with increased risk of type 2 diabetes, hypertension, and coronary artery disease (Freedman et al., 2001). Being overweight as a child also increases the risk of developing type 2 diabetes before age 21 (Sinha et al., 2002).

The best estimate of the prevalence of type 2 diabetes among those younger than 21 in the United States is about 0.1 percent based on National Health and Nutrition Examination Survey (NHANES) data from 1988-1994 (Fagot-Campagna, Saaddine, Flegal, & Beckles, 2001). Given the increase in overweight among children, it seems reasonable to assume that the prevalence now is higher than 0.1 percent—but by how much is unclear. Although type 2 diabetes may not be common enough for the NCS to examine with sufficient power, insulin resistance or closely related conditions, such as metabolic syndrome, are outcomes that would occur with sufficient frequency among subjects younger than 21 and could serve as both outcomes and markers for adult disease. Insulin resistance is considered the underlying abnormality in metabolic syndrome. Metabolic syndrome, according to the World Health Organization and as modified by Laaksonen et al. (2002), is defined by fasting hyperinsulinemia, impaired fasting glycemia or diabetes, and the presence of at least two of the following: abdominal obesity, dislipidemia (hypertriglyceridemia or low HDL cholesterol), or hypertension. Such a definition is feasible for detection in large-scale epidemiologic studies and identifies those who are at high risk of developing type 2 diabetes. The prevalence of metabolic syndrome among adults, as compared with the prevalence of type 2 diabetes, is about four-fold greater (Laaksonen et al., 2002). Investigations based on NHANES III data indicated that approximately 4 to 10 percent of adolescents ages 12-19 have metabolic syndrome (Cook, Weitzman, Auinger, Nguyen & Dietz, 2003). Thus, it is reasonable to assume that an outcome definition of metabolic syndrome like the definition presented above would have a prevalence rate above 0.2 percent. This means the NCS would have sufficient power to examine metabolic syndrome in relation to a wide range of exposure levels.

Mounting evidence suggests prenatal factors and early childhood experiences may influence the development of disease later in life (Barker, 1992). Altered fetal growth has been related to increased risk of cardiovascular disease, hypertension, and diabetes in adulthood (Barker, 1995; Barker & Osmond, 1986; Barker, Winter, Osmond, Margetts, & Simmonds, 1989; Poulter, Chang, MacGregor, Snieder, & Spector, 1999). Accelerated childhood growth is related to the risk of breast cancer in women (Ahlgren, Melbye, Wohlfahrt, & Sorensen, 2004) and to impaired glucose tolerance in adulthood (Hales et al., 1991).

1.2.1.6 Injury

Both unintentional injuries (e.g., motor vehicle crashes, suffocations) and intentional ones (interpersonal violence, child maltreatment, self-inflicted injuries) exert a tremendous toll in childhood. Beyond the first year of life, unintentional injuries are the leading cause of mortality in every age group until age 44 years (Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2007). In the teen years, homicide and suicide are the second and third leading causes of death, respectively. Fatal injuries represent only a small portion of the problem; it is estimated that in 2001 more than 230,000 children younger than 21 were hospitalized for an injury and approximately 9.7 million were treated in an emergency room and released (Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2007). The economic burden of injuries for persons of all ages was estimated at $406 billion in 2000, including $80.2 billion in medical care costs and $326 billion in

lost productivity (Finkelstein, Corso, & Miller, 2006). For children and adolescents younger than 14, the total economic burden in 2000 was estimated at more than $50 billion.

Similar to other outcomes, injuries result from exposures in multiple domains and represent the convergence of individual behaviors (e.g., risk taking, aggression), the physical environment (e.g., road embankment, access to weapons), and societal factors (e.g., access to emergency care). Many serious injuries result in significant impairment with lifelong consequences for health and development. From this perspective, injuries are not only an important outcome to investigate in the NCS, but also an exposure that alters trajectories of development in multiple outcome domains of interest. This could occur through direct effects (e.g. a head injury causing direct brain damage) or through more subtle pathways (e.g., the emotional effects of the event leading to post-traumatic distress; changes in level of physical activity due to physical limitations imposed by injury).

Haddon and other injury prevention pioneers conceptualized injuries as the consequence of human exposure to energy in ways that resulted in an injury (Haddon, 1964; Stapp, 1957). This idea expanded the field to analysis and study of physical forces and how to modify their impact on humans as a conceptual framework for the control and prevention of injuries (Haddon, 1970). Identification of the combination of individual, environmental, and societal factors that result in injury is critical for the development of effective interventions. Childhood injury prevention experts recommended conducting longitudinal cohort studies to identify environmental risk and contextual factors and understand how they can be modified to reduce injuries (Committee on Injury and Poison Prevention, 1996; Scheidt, 1988). Careful analyses of multiple conceptual frameworks for injury prevention emphasize that a temporal perspective and acknowledgement of the complex interplay of societal and environmental factors are critical (Andersson & Menckel, 1995). Thus, moving beyond the surveillance and cross-sectional methodologies (Scheidt et al., 1995) to longitudinal studies of sufficient size is essential to separate confounders and isolate causal relations that can provide the basis of effective preventive strategies (Rivara, 1999).

1.2.1.7 Reproductive Development

Hypospadias is one of the most common congenital anomalies, affecting 27-55 of every 10,000 births in the United States (Paulozzi, 1999; Paulozzi et al., 1997) or 0.8 percent of male live births (Pohl et al., 2007). Cryptorchidism affects 3 percent of full-term male newborns (up to 7.7 percent of low birth weight infants) decreasing to about 1 percent by age 1 (Pohl et al., 2007). Reports of increasing trends for hypospadias (Paulozzi, 1999; Paulozzi et al., 1997) and cryptorchidism (Paulozzi, 1999) in the United States and other countries and secular trends toward decreasing age at menarche and other measures of puberty onset in boys and girls (Herman-Giddens et al, 1997; Herman-Giddens, 2006; Kaplowitz et al., 2001; Lee et al., 2001), have created concerns about the etiological factors behind these trends. These factors include better nutrition or perhaps over-nutrition; earlier and greater growth; increasing incidence of obesity; and socioeconomic or environmental factors.

Documented exposures of children and pregnant women to compounds that have potential reproductive toxicity support the importance of studying environmental determinants of age at puberty. Exposure of children and pregnant women to hormonally-active agents (HAAs, also called endocrine disruptors) is widespread in America (CDC, 2003), and animal studies suggest the potential for toxicity at current levels of exposure (Vom Saal & Hughes, 2005). For example, cross-sectional data from NHANES III (Selevan et al., 2003; Wu et al., 2003) suggest that higher blood lead levels may be associated with a delay in the onset of puberty in girls, paralleling similar findings in animals. Precocious puberty was reported in girls who were both exposed in utero to the fire retardant FireMaster, which contained polybrominated biphenyls (PBBs), and breast-fed by mothers who were exposed to the fire retardant

(Blanck et al., 2000). Bisphenol A, a weak estrogen (Pottenger et al., 2000), is a high production volume chemical used in a variety of applications, including manufacturing flame retardants, resins, and plastics. Human exposure may arise in a number of circumstances, for instance, when foods are contaminated by heated plastics. Blood levels of bisphenol A in pregnant women (Schonfelder et al., 2002) are similar to those found in pregnant rats that give birth to offspring with bisphenol A-induced reproductive toxicity (Howdeschell, Hotchkiss, Thayer, Vandenbergh, & vom Saal, 1999; Pottenger et al., 2000; Rubin et al., 2001). Atrazine is a widely used herbicide. In a population-based probability sample of children ages 3-13, about 3 percent of children had detectable levels of an atrazine metabolite in their urine, and urban-rural differences in levels were not statistically significant. Recent experiments in peripubertal rats show that atrazine in doses of 30 milligram per kilogram orally per day for as long as 25 days delayed the onset of puberty (Ashby et al., 2002). It is not clear if the doses effective in animal experiments result in urinary metabolite levels like those seen among children with detectable levels.

Lack of accurate information on the level and timing of past exposures to HAAs has limited most previous studies of the potential human impacts of known and suspected HAAs. This limitation will be directly addressed by the prospective design of the NCS because exposures to chemicals will be measured during pregnancy, in breast milk, and in the perinatal period before the appearance of health effects. The measurement of multiple outcomes related to single, multiple, and continuous or repeated exposures is only possible with a large longitudinal study. The potential for cumulative effects on the reproductive system can only be discerned through the use of a large longitudinal sample that allows repeated measures of exposure and evaluation of reproductive outcomes through time. Measures or biomarkers of exposure are available for most HAAs of interest and will allow linking of exposures at specific life stages with early or late reproductive outcomes. Measures of gene prevalence and gene expression will permit examination of genetic polymorphisms that may influence gene-environment interactions and will allow assessments of genetically determined inter-individual differences in susceptibility to HAAs.

Since the effects of HAAs are gender specific, it will be necessary to study exposure-outcome links separately in males and females, which will reduce the sample size for each case to approximately 50,000. Susceptible subgroups related to genetic polymorphisms may require additional subgroup studies.

1.2.2 Environmental Factors That May Influence Childhood Chronic Conditions

This section provides the rationale for emphasis of the NCS on an array of environmental factors and their impacts across domains and time. These include the natural and built environments with their attendant chemical, physical, and biological factors; the social environment; individual behaviors; biological factors; and genetics. It should be emphasized that health states are determined by interactions among genetic and non-genetic factors, and that these interactions may change over time.

1.2.2.1 Chemical Exposures

There is increasing and ample evidence that children experience a significantly greater vulnerability to the effects of chemical exposures than do adults in similar environments (Anderson, Diwan, Fear, & Roman, 2000; International Programme on Chemical Safety [IPCS], in press). A National Academy of Sciences Committee on Pesticides in the Diets of Infants and Children identified four fundamental differences that contribute to children's heightened susceptibility to toxic chemicals (National Research Council, 1993): (1) Children have disproportionately heavy exposures to environmental toxicants as a consequence of their greater intake kilogram-for-kilogram of food, water,

and air coupled with their unique behaviors, in particular their oral exploratory behavior in infancy; (2) Children's metabolic pathways, especially in the first months after birth, are immature. In many instances, children are less able than adults to excrete and/or detoxify toxic compounds; (3) Children are undergoing rapid growth and development, which makes them more vulnerable to environmental toxicants; (4) Children have more years ahead of them to develop chronic diseases that may be initiated by their exposures than do adults. Although broad windows of sensitivity during development can be identified for many systems, information on exact timing of sensitivity, and on any preventable factors, is limited. This lack of information reinforces the importance of detailed exposure assessment.

The chemical environment in which children live has also changed with regard to known risks of several decades ago (Lioy, 1999; National Research Council, 1991). Today there are more than 80,000 synthetic chemicals, most developed since the 1950s (Environmental Protection Agency [EPA], 1998a). These include plastics, pesticides, fuels, building materials, antibiotics, chemotherapeutic agents, flame retardants, and synthetic hormones. Children are at especially high risk of exposure to the 2,800 synthetic chemicals produced in quantities of one million tons or more per year (Environmental Protection Agency, 1998b). These high-production-volume (HPV) chemicals are the synthetic materials dispersed most widely in air, food, water, and consumer products in homes, schools, and communities (EPA, 2001). Recent national surveys show quantifiable levels of HPV chemicals have been detected in the bodies of most Americans as well as in the milk of nursing mothers (EPA, 2003).

Although much remains to be learned about associations between the environment and disease in children, accumulating evidence suggests chemical, physical, and biological factors contribute to disease causation and severity. Numerous pollutants in the indoor environment—second-hand tobacco smoke, mold and mites, cockroach droppings, animal dander, and certain pesticides (CDC, 2005; Gergen et al., 1999)—have been identified as triggers for childhood asthma. Reduction in children's exposures to these indoor pollutants has been shown to reduce frequency of asthma (Lioy, Freeman, & Millette, 2002). Evidence indicates that ambient air pollutants—fine particulates, ozone, oxides of nitrogen, and diesel exhaust—also increase the incidence of asthma and trigger asthmatic attacks (Kattan et al., 2005; Salam, Li, Langholz, & Gilliland, 2004). Reduction in ambient air pollution has been associated with reduction in the number of hospitalizations due to asthma and other respiratory diseases (Friedman, Powell, Hutwagner, Graham, & Teague, 2001; Gauderman et al., 2004; Suh, Bahadori, Ballarino, & Spengler, 2000). Drinking water may have low-level concentrations of a number of chemical contaminants, such as pesticides, phthalate plasticizers, and byproducts of water disinfection. Animal studies indicate that some of the phthalate plasticizers have anti-androgenic properties and may cause birth defects (Blount et al., 2000; Barlow et al., 2003). Childhood cancer has long been linked to ionizing radiation. More recently, benzene, 1, 3-butadiene, and pesticides have been etiologically associated with childhood malignancies (Andrade et al., 2006; Daniels et al. 2001). A recent National Academy of Sciences study suggests that at least 28 percent of developmental disabilities in children may be caused by environmental contaminants acting alone or in combination with genetic factors (Bigbee et al., 1999; Lee, Cantor, Berzofsky, Zahm, & Blair, 2004; National Academy of Sciences, Committee on Developmental Toxicology, 2000; Slotkin, 1999). Although the concentrations of such contaminants may not be sufficiently high to cause overt acute toxicity among exposed individuals, the safety of low-level exposures to such chemicals in utero or during early childhood is unclear and is a serious concern.

The various routes and patterns of exposure in the environment can impact internal absorption and biological effects (EPA, 1998). Very little research is available about differences in patterns of exposure (e.g., short-term, peak, cumulative, chronic, or intermittent). The importance of considering exposures to a single or mixture of chemicals through all relevant pathways and routes as an aggregate exposure is exemplified by studies of chorpyrifos (IPCS, in press), lead (Albalak et al., 2003; Garcia Vargas et al., 2001; Morgan et al., 2005), arsenic (Pineda-Zavaleta et al. 2004), and DDT for malaria control (Carrizales et al., 2006; Diaz-Sanchez, Rumold, & Gong, 2006). These studies report high

levels of exposure from multiple routes with the largest contributor sometimes resulting from unexpected sources. How different patterns of exposure, such as peak exposure or cumulative exposure from all sources and pathways through time, determine the overall risk to individuals is not well understood (Herrera, Ochoa, Franco, Yanex, & Diaz-Barriga, 2006). Some studies of organophosphate pesticides (OP) point to greater susceptibility to cumulative exposure to OPs in children compared to adults (IPCS, in press). Thus far, however, the measurement methodology, capability, and adequate study size have not been available in any study to begin to understand the impact of routes and patterns of exposures (Wessels, Barr, & Mendola, 2003).

1.2.2.2 Physical Exposure: The Built Environment

The physical environment in which children live has prompted concerns about potential health effects. A higher proportion of children in America live in cities and suburbs than ever before, and the built environment has been shown to be capable of influencing children's physical and mental health and their risk of disease (EPA, 2003; Department of Agriculture, 2003; Frumkin, 2002; Galvez, Frieden, & Landrigan, 2003; Horowitz, Colson, Hebert, & Lancaster, 2004; Jackson, 2003). The adverse effects of the modern built environment are magnified in low-income, predominantly minority, urban communities where crowded streets, lack of outdoor play-spaces, limited access to fresh and healthy food, and substandard housing contribute to substantial and well-documented disparities in health (Morland, Wing, & Diez-Roux, 2002; Morland, Wing, Diez-Roux, & Poole, 2002; Sallis, Bauman, & Pratt, 1998; Sallis, Kraft, & Linton, 2002; Sallis et al., 1990). Recognition is increasing that characteristics of the built environment may influence diet and activity patterns and, as a result, increase the risk of obesity (Ewing, Schmid, Killingsworth, Zlot, & Raudenbusch, 2003; Frank, Andressen, & Schmid, 2004). Humpel et al. (2002) observed that physical environmental factors show consistent associations between the built environment and physical activity behavior. They also noted that availability of and access to bicycle paths, footpaths, health clubs, and swimming pools, as well as favorable aesthetics (e.g., indicating that it is pleasant near the home) are associated positively with physical activity. Thus, the physical environment is an important predictor of physical activity change and related health outcomes (Berrigan & Troiano, 2002; Berrigan, Troiano, McNeel, Disogra, & Ballard-Barbash, 2006). Physical activity of youth appears to be determined by many factors, including the physical environment, but the long-term influence of the built environment on children's physical activity is largely unexplored with about 75 percent of the extant literature being cross-sectional in nature (Sallis, Prochaska, & Taylor, 2000). A more recent review shows that physical activity in childhood exerts its strongest influence in diseases that have in common altered stress, inflammation, and leukocyte function, such as asthma and arthritis (Schwarzenberg & Sinaiko, 2006; Van Gaal, Mertens, & De Block, 2006). The impact of physical activity on critical periods of development in children need not be limited to the walking child, since assisted exercise in preterm infants has been shown to increase body weight and improve bone strength.

1.2.2.3 The Psychosocial Environment

The psychosocial environment plays a critical role in healthy development. Substantial evidence points to the complex and dynamic role that psychological and social environmental influences play in development, and in the creation and amelioration of health disparities. Concentrated poverty, racial segregation, and high levels of crime contribute to poor health, developmental deficits, and high levels of risk behaviors among individual residents (Aneshensel & Sucoff, 1996). Yet to be explored are the mechanisms and the interactions with genetic and other exposure factors needed to guide interventions. National and local public policies influence the resources available to individuals and families and their ability to manage health-related aspects of their lives. The functioning of families, the

most crucial element of the psychosocial environment for young children, is affected by economic, policy, social, and cultural dimensions of the environment.

Evidence and practical experience attest that parenting practices, as just one critically important component of a child's psychosocial environment, can have a profound impact on a child's development and outcome (Borkowski, Ramey, & Bristol-Power, 2002). There is an increasing body of evidence based on animal research which elucidates pathways that explain how early social environment can cause lasting changes in gene expression which remain into adulthood (Barr et al., 2004; Newman et al., 2005). It is also known that abuse and unstable parent-child relationships can lead to behavioral disorders and increased morbidity and mortality (Shonk & Cicchetti, 2001; U.S. Department of Health and Human Services, 2004). Suomi's (2004) research demonstrates that in non-human primates marked differences in maternal nurturing interact with genetic variations in certain neurotransmitters resulting in dramatically different outcomes for the offspring. This suggests mechanisms for human behavioral development, and potential avenues for targeted interventions in humans (Champoux et al., 2002; Suomi, 2004). The observation that certain parenting styles are associated with a young child's risk of being overweight creates important questions about identifying the mechanisms for this association and its interactions with genetic and other factors. Understanding these gene-social environment interactions is both a pressing need and an emergent opportunity (Tholin, Rasmussen, Tynelius, & Karlsson, 2005) that can best be addressed by the National Children's Study.

Psychosocial environmental influences appear to interact with physical and chemical exposures in complex ways. Environmental justice literature (Brulle & Pellow, 2006; Bullard, 1983; Bullard, 1990; Bullard & Wright, 1993) suggests that the impact of exposure to toxic substances may be greater in communities that have low levels of education and have poor access to health services. Social factors may also confound relations between physical exposures and health. For example, an association between exposure to an environmental toxicant and violent behavior may be misinterpreted as causal when, in fact, poverty causes the physical exposure and violence. Social factors and physical exposures may also modify or mediate the effects of one another on health outcomes. Sorting out these influences is essential if researchers are to understand why some children are healthy and thrive while others do not.

1.2.2.4 Biological Factors

A child's biologic environment ranges from in utero interaction with maternal physiology to nutritional, infectious, and allergenic exposures throughout childhood and adolescence. Accurate serial assessment of a child's multifaceted biologic exposures is important to understand the etiology and severity of NCS outcomes from preterm birth and congenital anomalies to insulin resistance and schizophrenia in adolescence.

Infection, inflammation, and stress

Maternal or early childhood exposure to many different organisms has been implicated in the subsequent development of outcomes to be studied in the NCS, including preterm birth (Andrews, Hauth, & Goldenberg, 2000; Goepfert et al., 2004; Pararas, Skevaki, & Kafetzis, 2006), neurodevelopment and psychiatric disorders (Hagberg & Mallard, 2005; Rapoport, Addington, Frangou, & Psych, 2005), and asthma (Garcia-Garcia et al., 2007; Sigurs et al., 2005). In contrast to the direct suppurative effects of infection, such as the cognitive and hearing losses associated with bacterial meningitis, the nature and timing of some putative associations suggests the distal influence of host inflammatory mediators produced in response to infection. However, the nature of the relation between in utero exposure to infection or inflammation and subsequent outcomes has been difficult to study in humans. For example,

the epidemiological literature suggests a strong association between maternal viral infection and subsequent schizophrenia in offspring (Bagalkote, Pang, & Jones, 2001; Yolken & Torrey, 1995). Animal studies demonstrate that in utero or early life exposure to circulating cytokines result in neuronal lesions compatible with schizophrenia (Gilmore, Jarskog, Vadlamudi, & Lauder, 2004; Meyer et al., 2006). Establishing a direct relation between prenatal inflammatory exposure and subsequent schizophrenia has been impossible because of time lags between exposure and outcome, which limit potential preventive and therapeutic strategies. The potential relation between in utero inflammation and autism has similar characteristics (Chauhan & Chauhan, 2006; Meyer et al., 2006), and the ability of the NCS to capture these early exposures offers similar opportunities for advancing etiologic understanding and prevention and treatment possibilities.

The relation between early infection or inflammation and asthma poses additional questions concerning the influence of immune response and subsequent disease. Numerous studies suggest that viral infection during infancy is associated with increased asthma risk (Garcia-Garcia et al., 2007; Sigurs et al., 2004). A related body of literature that is often presented under the rubric "hygiene hypothesis" suggests early exposure to infectious products, perhaps bacterial products in particular (Braun-Fahrlander et al., 2002), protects against subsequent development of asthma. Attempts to untangle this relation have focused on the impact of type and timing of infection on development of a strong Th-1 lymphocyte response as opposed to the persistence of Th-2 immunologic response associated with asthma and atopy (Effros & Nagaraj, 2007). Recent studies have suggested this is complicated even further by the timing of exposure to non-infectious allergens such as dust mite or animal dander (Holt & Sly, 2002).

An additional contributor to immune system development is exposure to maternal stress unrelated to infection and inflammation (Elenkov, 2004; von Hertzen, 2002). Genetic variation in the structure or activity of specific molecular mechanisms, particularly Toll-like receptors, also seems to influence the already complex relations (Vercelli, 2006). Serial measures of maternal and child infection and inflammatory response, emotional and physiologic stress, timing of exposure to a variety of potential antigens, and genomic analysis within the NCS will be integrated to enable an increased understanding of asthma etiology and the potential to develop new preventive and ameliorative strategies.

Elevated maternal glucose or diabetes

Compared to infants born to women without diabetes, infants born to women with a diagnosis of diabetes or other evidence of elevated blood glucose have an increased risk of congenital anomalies (Farrell, Neale, & Cundy, 2002; Guerin, Nisenbaum, & Ray, 2007; Nielsen et al., 2005; Schaefer et al., 1997; Sharpe, Chan, Haan, & Hiller, 2005). The amount of additional risk varies depending on the nature of the diabetes and the degree of maternal hyperglycemia. This may suggest a simple dose-response mechanism. However, a range of disparate major and minor defects with different embryologic origins is influenced by maternal hyperglycemia (Schaefer et al., 1997; Nielsen et al., 2005). Animal models suggest that one potential pathway through which maternal hyperglycemia disrupts normal embryologic development is via oxidative stress damage following increased fetal glucose metabolism (Loeken, 2006). The fetal oxidative stress response can influence selective dysregulation of individual gene expression and have differential effects on organogenesis depending on the timing and degree of maternal hyperglycemia. This mechanism may explain the similar effects of maternal hyperglycemia on the development of multiple and diverse organ systems. The potential role of oxidative stress in the etiology of at least some birth defects also dovetails with possible mechanisms of other exposures to be investigated in the NCS including infectious and inflammatory sequelae, diet, and respiratory pollutants.

Diet and nutrition

Aspects of maternal and child diets that are important to multiple outcomes within the NCS include overall caloric and macronutrient intake and potential exposure to pesticides or other chemical contaminants. Collection of additional dietary information will enable elucidation of potentially more subtle influences of diet on health and disease.

For example, in both human and animal diets with a high glycemic index and glycemic load, measures of a food's post-consumption impact on blood glucose (Frost & Dornhorst, 2005) have been associated with increased risk of obesity and type 2 diabetes which is independent of the diet's caloric content (Ludwig, 2002; Pawlak, Kushner, & Ludwig, 2004; Schulze et al., 2004). Further understanding of these presumptive relations is necessary if optimal interventions to curb the increase of obesity and related morbidity are to be developed.

A nutritional factor that may play an important modifying or protective role in relation to multiple NCS outcomes is dietary anti-oxidants. Oxidative stress has been hypothesized to play an etiologic role in numerous outcomes, including neurodevelopment and psychiatric conditions (Chauhan & Chauhan, 2006; Meyer et al, 2006); asthma (Effros & Nagaraj, 2007); birth defects (Loeken, 2006); and diabetes (Duncan & Ines Schmidt, 2006; Esposito et al., 2002). Evidence from human and animal studies regarding the ability of diets high in antioxidants to protect against disease is mixed (Abela, Howe, Oakes, & Webster, 2005; Devereux et al., 2006; Litonjua et al, 2006; Murray, Simpson, Kerry, Woodcock, & Custovic, 2006). The potential benefits of such a diet, however, retain biologic plausibility. For example, culture studies suggest the ability of antioxidants to prevent neuronal damage, although the developmental timing is crucial (Perry, Norman, Litzburg, & Gelbard, 2004). The longitudinal collection of systemic nutritional measures and dietary characteristics starting in utero and continuing through adolescence may help elucidate the role of oxidative stress in diseases and offer potential interventions.

1.2.2.5 Genetic Factors

The past decade has witnessed a virtual explosion in the development and application of genomic methodology and research that have direct application to the NCS. The majority of common disorders in children and adults are now recognized as having a "complex" multifactorial etiology, wherein multiple genetic and environmental factors play a role in disease causation (Kelada, Eaton, Wang, Rothman, & Khoury, 2003; Moore, 2003; Zondervan & Cardon, 2004). It is the interaction or multiplicative effects, rather than the sum of these factors, that likely underlies disease risk. These complex relations require that studies of disease causation assess each of these multiple factors in a common cohort of individuals as opposed to assessing different factors in different cohorts. In addition, changes in epigenetic factors and the association with environmental factors necessitate a longitudinal approach. This requires the kind of comprehensive assessment of genetic and environmental risk factors for disease in the same individuals and the large number of study participants to provide adequate statistical power (Garcia-Closas & Lubin, 1999) proposed in the National Children's Study.

The sequencing of the human genome provides powerful research tools to identify genetic variation that contributes to health outcomes (International Human Genome Sequencing Consortium, 2001; Venter et al., 2001). In the past, association studies using candidate genes have been the mainstay of epidemiologic investigations of the role of genetic and environmental factors in children's health. More recently, rapidly changing and increasingly affordable technology and information from the International HapMap Project have made whole genome association studies using haplotype tagging single nucleotide polymorphisms (SNPs) a reality (The International HapMap Consortium, 2005). The HapMap project has lessened the task of measuring millions of SNPs by using linkage disequilibrium to identify a reduced set

of “tag” SNPs for capturing variation throughout the genome (Johnson et al., 2001; Wall & Pritchard, 2005). As affordable technology becomes available, complete sequencing of the genome of NCS participants will be possible. Emerging systems biology approaches to genomic analyses, which seek to understand how different biologic systems are interconnected (Bogyo & Cravatt, 2007; Li & Burmeister, 2005) and how both the components and their relations can change over time, will benefit from repeated phenotypic and genomic measures in the NCS.

The Study will also have the power to examine gene-environment interactions from a developmental perspective in a new way. It will provide the opportunity to evaluate specific genetic factors in subgroups of mothers, fathers, and children in the Study. It will be a rich source of data that can be used to investigate the mechanisms behind complex diseases such as autism and asthma, the quantitative contribution of genetic variation to common conditions such as obesity, and the impact of gene and environment interactions on behavior and health outcomes. Multiple gene-environment and gene-gene interactions play a key role, creating the need for complex, computer-intensive forms of analysis. The analysis of genomic data is a field of much active research (Chatterjee, Kalaylioglu, Moslehi, Peters, & Wacholder, 2006; Heidema et al., 2006; Thornton-Wells, Moore, & Haines, 2004). Analysis of genotype effects, multi-locus genotype-genotype interactions (e.g., epistasis), and gene-environment interactions can be conceptualized in a regression analysis framework for different types of outcomes where the predictor variables include SNP genotypes, environmental exposures, epistasis (e.g., interactions) among SNPs, and SNP-environment interactions. Methods developed for analyzing high-dimensional data such as microarray gene expression, massively parallel signature sequencing (MPSS), and evolutionary trees of haplotypes may also be utilized. New analytic methods can be expected to emerge in the future and researchers analyzing the NCS genomic data will apply the best methods available in every phase of the process.

1.2.3 Conclusion

There is a well established vulnerability to the effects of environmental exposures for the embryo, fetus, infant, young child, and even the developing adolescent. There is a broad array of environmental exposures that have been identified as possible threats to children’s health and development, only a few examples of which are noted above. Only for a small number of these exposures has empirical and theoretical evidence of their specific effects on children been established. Likewise, conditions and diseases in children that represent the major health threats of the new morbidity continue to challenge the researchers who seek to understand their genetic and environmental causes. The convergence of these experiences and scientific observations was a compelling rationale for the President’s Task Force to recommend, and for Congress to direct, that NICHD conduct a longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children’s health and development with a national scope, a large sample size, and a breadth of measures that are capable of identifying the environmental and genetic factors contributing to the major diseases and conditions that affect our children.