



FROM CELLS TO SELVES



Targeting Sudden Infant Death Syndrome (SIDS): A Strategic Plan



National Institute of Child Health and Human Development



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The NICHD Mission

The National Institute of Child Health and Human Development (NICHD) seeks to ensure that every individual is born healthy, is born wanted, and has the opportunity to fulfill his or her potential for a productive life unhampered by disease or disability. The Institute further strives to help parents have the children they want, at the times they want them, and to ensure that every mother experiences a pregnancy free of adverse complications, and that persons with physical or mental disabilities receive the maximum benefit of rehabilitation to allow them to function as fully as possible in society. Key to the success of this mission is answering the fundamental questions of how a single fertilized cell eventually develops into a fully functional adult human being and how a multitude of genetic and environmental factors influence that process for good or ill.

Programs at the NICHD are based on the concepts that adult health and well-being are determined in large part by episodes early in life, sometimes before birth; that human development is continuous throughout life; and that optimal outcomes of development are important not only to the individual but to society. NICHD research is also directed toward restoring or maximizing individual potential and functional capacity when disease, injury, or a chronic disorder intervenes in the developmental process. Thus, the NICHD mission truly spans the life cycle, and much of the health and well-being of our population depends on the success of the Institute's research.

The Strategic Planning Process

During 1998 and 1999, the NICHD staff engaged the scientific community in jointly developing a strategic plan to facilitate achieving its mission.

The initial framework document for this plan, *From Cells to Selves*, highlighted four areas for immediate strategic development and described a series of scientific goals under each area. These four areas were as follows:

- *Genetics and Fetal Antecedents of Disease Susceptibility* includes the interaction of the genotype with socioeconomic, environmental, and psychological factors in the fetal and postnatal environment that contribute to health or the pathophysiology of diseases.
- *Reproductive Health for the 21st Century* comprises the biological and behavioral factors that allow couples to have healthy children when they want them and the reproduction-related conditions that may affect women during and after their reproductive years.
- *Developmental Biology: Understanding Normal and Abnormal Development* consists of the basic biological science necessary to understand early development *in utero* and through the time when many organ systems form.
- *Biobehavioral Development* includes research to better understand the developmental processes involved in forming cognitive, learning, emotional, social, and physical behaviors, and the biological and environmental factors that make infants, children, and adolescents more susceptible to behavioral disorders or to adopting risk-taking and violent behaviors.

Health Disparities: Bridging the Gap, a fifth strategic plan, was developed to better understand how natural biological and behavioral forces interact with a variety of social, community, and economic factors to produce health disparities, and how to intervene to enhance the health and well-being of these minority and underserved populations.

In addition, at the request of the United States Congress, the NICHD produced strategic plans in 1989 and 1995 that summarized advances in Sudden Infant Death Syndrome (SIDS) research and made recommendations identifying the most promising avenues of research to be pursued over subsequent 5-year periods. In 1999, Congress recommended that the Institute develop a third 5-year plan. Since the NICHD has been engaged in strategic planning from 1998 to 2001, the planning process for the SIDS program was integrated with the development of other research agendas.

To formulate the new SIDS strategic plan, the NICHD convened a working group comprising distinguished scientists and health care professionals from around the country. (See Appendix.) In collaboration with NICHD staff, the working group identified and prioritized research goals and suggested strategies to meet those goals. The working group drew upon ongoing planning efforts, previous emphasis areas, recent forums, workshops, conferences, and research findings to develop a draft of the strategic plan for a SIDS research and public health agenda that would guide the Institute for the next 5 years.



FROM CELLS TO SELVES

The draft plan was posted on the NICHD Web site to allow members of advocacy groups, nonprofit organizations, the scientific community, and the general public to comment. In addition, the Institute shared the plan with members of the National Advisory Child Health and Human Development Council and with the Friends of the NICHD, a coalition of more than 100

professional and patient organizations committed to the Institute's scientific mission. After consolidating and reviewing all comments, the NICHD revised and finalized the plan. This document is intended as a targeted, but flexible, blueprint that can be modified as new scientific findings, research opportunities, or resources become available.

Introduction

SIDS occurs worldwide. In the United States alone, approximately 3,000 infants die each year from SIDS. The majority of SIDS deaths occur before infants reach 6 months of age. These deaths, although associated with a sleep period, are sudden and unpredictable. In most cases, infants appear healthy before succumbing to SIDS. No explanation for these deaths can be found, even when a complete postmortem is performed, including an autopsy, an examination of the death scene, and a review of the infant's clinical and family history. In the absence of an identifiable cause of death, these infants' deaths are, by standard definition, labeled SIDS.

SIDS exacts a devastating emotional toll on affected families and caregivers. In 1974, landmark legislation—the Sudden Infant Death Syndrome Act (P.L. 93-270)—gave the NICHD the statutory responsibility to oversee SIDS research. The Institute's ultimate goal is to eliminate SIDS. To reach this aim, it is important to understand the underlying causes and mechanisms of the syndrome, to develop strategies to identify infants at high risk for sudden death, and to develop and implement preventive strategies that can effectively reduce the incidence of SIDS across diverse populations.

Great progress has been achieved in understanding SIDS and reducing the number of deaths caused by this tragic disorder since the formulation of the first 5-year plan. The plans served to organize the efforts of researchers, clinicians, and Federal agencies. The decade's most significant accomplishments are as follows:

- Establishment of the *Back to Sleep* coalition and campaign;
- Revision of the SIDS definition and the development of death investigation guidelines to improve the scope and quality of information used to establish the diagnosis;
- Formation of tissue banks to facilitate studies of etiology and pathogenesis;
- Elucidation of the role of inborn errors of metabolism in sudden infant death and the incorporation of screening for disorders of fatty acid metabolism as a diagnostic tool at autopsy;
- Establishment of a system to monitor infant care practices and health outcomes associated with SIDS risk reduction interventions;
- Identification of unsafe bedding practices in the infant sleep environment;
- Delineation of the patterns of risk factors that contribute to the increased incidence of SIDS in specific minority populations;
- Assessment of current methods of cardiorespiratory monitoring to identify useful physiologic markers of SIDS risk; and
- Discovery of the neurologic abnormalities unique to SIDS infants and exploration of how they may place an infant at risk.

The specific advances in knowledge are described in the background sections located throughout the plan.

Less than a decade ago, almost twice as many American infants were dying of SIDS than is the case today. By the early 1990s, the practice of placing

infants to sleep on their stomachs had been identified as a significant risk factor. The subsequent recommendation by the American Academy of Pediatrics to place healthy babies on their backs to sleep (side as an alternate position) and the success of the NICHD-led national *Back to Sleep* campaign are associated with a large decrease in the number of infants placed to sleep on their stomachs and a 40-percent reduction in SIDS rates between 1992 and 1998. As a result, about 2,000 fewer babies now die each year than was the case in 1992. However, SIDS still remains the leading cause of death in infants between 1 month and 1 year of age in the United States. Moreover, significant disparities in SIDS prevalence rates still exist among various racial and ethnic groups.

The purpose of this strategic plan is to build on past successes and forge new paths of discovery. The recommendations go beyond deaths labeled as SIDS by

medical examiners and coroners to include all sudden deaths occurring from late fetal life through infancy and early childhood. The plan defines strategies aimed at improving maternal as well as infant health. It encompasses both basic infant care practices and research based on the latest molecular genetic technologies. This framework will provide researchers with the knowledge and resources needed to illuminate the etiology of SIDS and, ultimately, to eliminate these needless deaths.

The plan is divided into four sections: Etiology and Pathogenesis, Prognostics and Diagnostics, Preventive Strategies, and Health Disparities. Each section contains a statement of the problem, background information, and specific recommendations designed to address gaps in our current state of knowledge or intervention activities and to correct deficiencies in our basic scientific infrastructure.

Etiology and Pathogenesis

Knowledge acquired during the past decade supports the general hypothesis that infants who die from SIDS have abnormalities at birth that render them vulnerable to potentially life-threatening challenges during infancy. The recommendations in this section are targeted toward understanding the following circumstances:

- How the neural abnormalities observable in SIDS infants develop;
- How these neural abnormalities affect infant health and development before and after birth;
- Whether there are genetic factors that predispose infants to sudden death; and
- How specific characteristics of the fetal and postnatal environment either contribute to the pathologic process or serve to protect infants.



We know that SIDS is a developmental disorder: it originates during fetal development and occurs within a distinct developmental window. Ongoing research into the basic mechanisms governing normal development, utilizing the latest technologies, will provide us with an essential basis for understanding how developmental processes go awry in SIDS infants. This approach is founded on the basic principle that understanding normal developmental processes is an essential prerequisite for understanding derangements in development, a principle which is strongly emphasized in another of the Institute's strategic plans, *Developmental Biology: Understanding Normal and Abnormal Development*. We also know that the health of the fetus determines the health of the infant—another fundamental principle reiterated in several current NICHD strategic plans, most notably *Genetics and Fetal Antecedents of Disease Susceptibility* and *Biobehavioral Development*. The biological continuum linking fetal and infant health or disease are carefully explored throughout this SIDS strategic plan.

Prognostics and Diagnostics

The development of fetal and neonatal screening tools to identify fetuses and infants at high risk of sudden death depends upon knowing—or at least having a strong indication of—the functional abnormalities that are responsible for death. Such knowledge is also necessary for the development of effective therapies for at-risk infants. Advances in the realm of prognostics and diagnostics are likely to create new opportunities for refining ongoing investigations into the etiology and pathogenesis of SIDS. Although a slow process, as one knowledge base grows so does the other. The recommendations in this section address the assessment of neural maturity and the development and predictive value of screening tools.

Preventive Strategies

As often happens in public health, it is possible to intervene successfully in the disease pathway and to reduce morbidity or mortality without a full understanding of the pathologic mechanism(s) involved. During the next 5 years, we wish not only to bolster the success of the *Back to Sleep* campaign but also to diminish the prevalence of other SIDS risk factors.

The recommendations in this section emphasize the need for

- Strong community partnerships;
- Knowledge of cultural variations;
- Rigorous evaluations of interventions and feedback from the lay community;
- Comprehensive and consistent assessments of fetal and infant deaths; and
- An understanding of how multiple risk factors may interact.

The need to build and maintain viable collaborative partnerships with communities is a central theme of another of the Institute's strategic plans, *Health Disparities: Bridging the Gap*. A recognition of the essential value of collaborations among all the stakeholder communities informs not only this section of the SIDS strategic plan but also the following section.

Health Disparities

Although SIDS rates have declined in all populations throughout the United States during the last decade, disparities in SIDS rates and in the prevalence of risk factors remain evident in certain groups. On a national level, SIDS rates are highest among American Indians, Alaskan Natives, and African Americans, and lowest among Asians, Pacific Islanders, and Hispanics.

However, prevalence rates vary within these groups based on socioeconomic factors. The recommendations in this section emphasize the following factors:

- The creation and maintenance of strong community resources for research and intervention;
- The investigation of both protective and adverse forces operating within and across populations;
- The investigation of both macro (e.g., equity of care) and micro (e.g., genetic predisposition) forces operating within and across populations.



The Concept of “Risk” in SIDS Research

The principal aims of this strategic plan are to focus research resources and effort into scientifically identifying risk factors for SIDS and to develop intervention strategies that reduce the occurrence of these tragic deaths. Many people have trouble understanding the concept of “risk.” As it is defined by epidemiologists, risk refers to the *probability* that an outcome will occur given the presence of a particular factor or set of factors.

Risk factors are identified through specific associations with the outcome, and their contribution is expressed as either decreasing or increasing the probability that the outcome will occur. Scientifically identified associations between risk factors (e.g., socioeconomic characteristics, behaviors, or environmental exposures) and outcomes, such as SIDS, do not necessarily denote causality. Other explanations for the association must be considered, and the mechanisms underlying the risk factor need to be delineated. Furthermore, as discussed in this report, the best current working model of SIDS suggests that more than one scenario of pre-existing conditions and initiating events may lead to SIDS.

Therefore, when a SIDS death occurs, it is important to focus on all of the risk factors that may be involved. Our goal is to develop knowledge that helps families and caregivers provide the best supportive environment for their children. We also wish to help families who have experienced a SIDS death better understand what has happened and why. We hope that this knowledge will help SIDS families heal.

Etiology and Pathogenesis

Statement of the Problem

Although deaths from SIDS still occur in this country every day and we do not yet know its cause or causes, we begin the millennium with tremendous excitement about the great strides that have been made in SIDS research over the past three decades. Almost three decades ago, Congress passed landmark legislation that gave the NICHD responsibility for SIDS research. Since then, Institute-supported multidisciplinary teams of medical and scientific investigators have focused on five major areas in SIDS research: (1) the brain and homeostatic control, (2) autonomic development and function, (3) infant care and the sleep environment, (4) infection and immunity, and (5) genetics.

As we have acquired more knowledge, it has become clear that these five broad areas of research are even more relevant to a full understanding of the etiology (cause) and pathogenesis (development of the disease process) of SIDS than was suspected at the beginning of these decades-long research efforts. What we now know about the relationships between each of these research areas and SIDS is detailed in the background material introducing each of the following subsections. One major goal of the 2001 Strategic Five-Year Plan is to eradicate **all** SIDS deaths through understanding the etiology and pathogenesis of the syndrome. Moreover, focusing the five major areas of research on possible cause(s) of SIDS is likely to result in the development of more specific—and hence, more effective—prognostic, diagnostic, and preventive strategies than are now available.

An overall “driving” hypothesis guiding SIDS research—now commonly referred to as the “triple-risk hypothesis”—has emerged during the past 30 years of investigations into the syndrome’s etiology and pathogenesis. This hypothesis, resulting from a synthesis of the knowledge gained from separate investigations, has been advanced in different ways and gradually refined by many different researchers.

According to the triple-risk hypothesis, SIDS occurs when three events impinge upon an infant simultaneously: (1) an underlying vulnerability in homeostatic control, (2) a critical developmental period in state-related homeostatic control, and (3) an exogenous stressor(s) that exacerbates the infant’s underlying vulnerability. Homeostasis includes the vital functions of blood pressure control, heart rate, respiration, chemoreception, upper airway reflexes, and thermoregulatory control, as well as the return of these functions to normal after stress has occurred. The underlying vulnerability puts an infant at risk for sudden death when he/she passes through the critical developmental period and encounters an exogenous stressor (e.g., stomach sleeping position). The triple-risk hypothesis explains, for example, why all infants do not die when placed in the stomach sleeping position (i.e., they do not have the underlying vulnerability), and why an exogenous stressor (e.g., stomach sleeping position) can be eliminated and thereby reduce mortality without our understanding the cause of the underlying vulnerability (etiology and pathogenesis). While most investigators perceive an underlying vulnerability in the infant, some investigators contend that healthy infants also are at risk during the unstable, rapidly changing developmental period in homeostatic control and when faced with a life-threatening stress.

The past 30 years of research have been particularly exciting because different investigations have provided compelling evidence in support of the triple-risk hypothesis. We have learned that (1) the underlying vulnerability most likely resides within the nervous system, which regulates homeostatic control, (2) the critical period likely relates to the development of the nervous system, and its interactions with other physiological systems, e.g., immunologic, cardiovascular, and respiratory systems, and (3) exogenous risk factors most likely interact with neural mechanisms that protect the infant from life-threatening events. Moreover, there may be a continuum of sudden death in early life that encompasses the last weeks of gestation (stillbirths) and the first year of life (SIDS). Epidemiologic studies have shown that the underlying vulnerability may result from an adverse fetal exposure to cigarette smoke. Neuropathological studies indicate that the vulnerability may be due to a deficiency in a serotonergic network of the brainstem in many SIDS infants, thereby affecting regions of the brain involved in homeostatic control. Developmental behaviorists have identified clinical markers of autonomic function, arousal, and behavioral maturity in infants. Laboratory physiologists have demonstrated that the first 6 months of life, the major risk period for SIDS, are a critical period for the development of homeostatic mechanisms and learned protective behaviors in all infants. Epidemiologists and laboratory physiologists point to exogenous stressors in the risk for SIDS, e.g., asphyxia from the face-down sleeping position, soft bedding, infection, and hyperthermia. A very important but still-unanswered question is the role of genetic factors in the etiology of SIDS, particularly possible interaction(s) between genetic and environmental factors.

We have learned that SIDS is an extraordinarily complex problem, and eliminating SIDS requires a multidisciplinary approach involving the efforts of pediatricians, epidemiologists, pathologists, neuroscientists, geneticists, infectious disease experts, nurses, and investigators in the

behavioral and social sciences, as well as other disciplines. We have learned that daily infant-care practices play a critical role. In addition, we have made extraordinary technical advances in all fields, including, for example, infectious diseases, with molecular screening for microbial agents; genetics, with the human genome project; and neuroscience, with modern techniques for application directly to the human brain. Thus, the groundwork is laid for major progress during the next 5 years of SIDS research.

The Brain and Homeostatic Control

Background

- SIDS brains may look “normal” with conventional neuropathological techniques at autopsy. Powerful research tools in quantitative neuroanatomy and neurochemistry, however, have uncovered important abnormalities within and above the brainstem in SIDS brains.



- These include deficits in serotonin receptors in the medullary raphe, the arcuate nucleus, and related regions of the brainstem, along with structural and developmental delays in the cerebellum. All of these regions have a common embryonic origin in fetal life.
- Other brain abnormalities reported in SIDS babies include heavy brain weight, white matter injury and developmental delay, and structural and neurochemical abnormalities in the hypoglossal nucleus, a region involved in the control of the airway during waking and sleeping.
- It is unclear how all these findings relate to each other because they have not all been studied in the same brains. However, many of these findings are in regions related to homeostatic control, and their discovery in SIDS brains represents a critical first step.
- Brainstem regions in animals that are likely homologous with the human arcuate (ventral medulla) and raphe regions are known to be involved in the development and control of breathing and blood pressure, thermoregulation, sleep and arousal, and the modulation of sensory and motor activity.
- Abnormal respiratory reflexes may explain the greater susceptibility to SIDS when infants are sleeping on their stomachs. Rebreathing of exhaled gas rich in carbon dioxide and poor in oxygen may fail to arouse and stimulate an infant with deficient chemoreception. Laryngeal receptors that cause apnea are more likely stimulated by reflux when the infant is in the prone position, an undesirable effect that may be exaggerated by brainstem abnormalities in the control system.
- Abnormal thermoregulation and sleep architecture may also contribute to risk because infants who sleep on their stomachs lose heat less effectively and experience fewer arousals.

Goals and Objectives

Goal: Elucidate the origin and range of brain abnormalities in SIDS and other forms of sudden death and reveal how these abnormalities are interrelated.

- **Objective:** Investigate the development of human brain regions involved in homeostatic control during gestation and early infancy, using neuroanatomic, neurochemical, cellular, and molecular techniques.
- **Objective:** Investigate the development of regions involved in homeostatic control in SIDS brains compared with postconceptionally age-matched control brains, including regions that have not been adequately tested with research tools—e.g., the hypothalamus, arousal systems, and the cerebellum—using neuroanatomic, neurochemical, cellular, and molecular techniques. Compare lesions [collected and studied] before and after the beginning of the *Back to Sleep* campaign.
- **Objective:** Study cerebral white matter abnormalities indepth in SIDS infants, including subtle gliosis, periventricular leukomalacia, lipid-laden macrophages, and hypomyelination. Attempt to correlate resultant findings with known biochemical deficiencies and histories of perinatal hypoxia and ischemia.
- **Objective:** Assess the effects of environmental insults known to put infants at risk for SIDS on human fetal brain development. These environmental insults include prenatal exposures to tobacco smoke and alcohol.
- **Objective:** Analyze the neuropathology of known diseases of autonomic function—e.g., Prader-Willi, Congenital Central Hypoventilation Syndrome (CCHS)—for clues to guide the further analysis of SIDS brains. Clues derived from these known autonomic disorders will come from functional brain imaging.

- **Objective:** Investigate the neuropathology of unexplained antepartum stillbirths in order to understand the relationship between such stillbirths and SIDS.

Goal: Understand the neurobiology of homeostatic processes, especially during different states of arousal and during development.

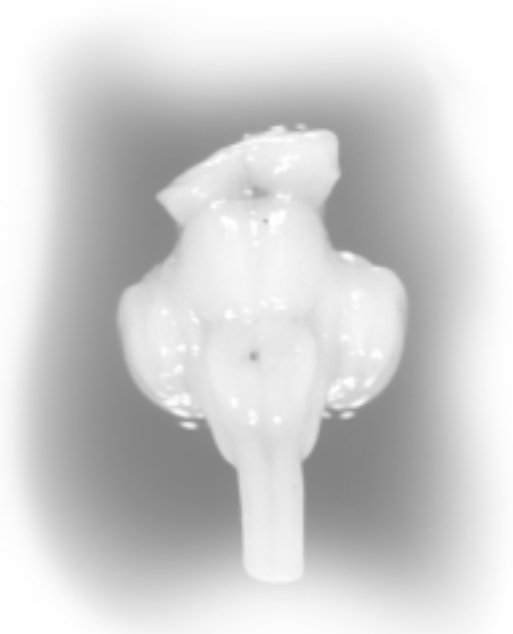
- **Objective:** Evaluate the functions of the ventral medulla and the medullary raphe in homeostatic regulation during various stages of development, beginning in fetal life. The degree of abnormal serotonin receptor binding and exclusivity to a substantial subset of SIDS victims provides a valuable clue; however, our current knowledge of the basic neurobiological role of the medullary raphe in a variety of homeostatic processes is incomplete.
- **Objective:** Evaluate the role of homeostatic processes in nervous system development. Genetically engineered or mutant animal models will prove useful for this endeavor.
- **Objective:** Investigate the functional maturation of sleep and arousal and how the arousal state influences homeostatic physiologic control.
- **Objective:** Investigate the interactions among homeostatic control systems because SIDS and related types of sudden death are likely to result from the inadequate function of more than one neurobiological process.
- **Objective:** Model and study lethal scenarios and protective reflexes, such as the laryngeal chemoreflex, during development. Investigate the possibility that presumably homeostatic processes or protective responses, if exaggerated by the malfunction of modulatory neurons or initiated at an inopportune time, may become maladaptive.

- **Objective:** Further define the central nervous system sites of physiologic dysfunction by integrating postmortem findings with physiologic studies in both humans and animals.

Autonomic Development and Function

Background

- The autonomic nervous system (ANS) regulates many of the rescue responses to potentially life-threatening events, including responses to respiratory, cardiac, thermal, and blood pressure challenges. These cardiorespiratory challenges frequently occur during sleep and during transitions between sleep states.



- ANS dysfunction and/or an altered trajectory in the development of this system are features found in many infants who have subsequently succumbed to SIDS. This ANS dysfunction appears to arise before birth owing to a compromised fetal environment.
- The peak incidence of SIDS occurs during a period of major reorganization of the autonomic nervous system. Measures of autonomic control show dramatic changes and instability during this transition period.
- An infant's defensive behaviors to respiratory challenges, such as rebreathing expired air, are compromised in the facedown position or when covered by loose bedding. Vulnerable infants also may have altered responses to changes in oxygen levels associated with sleeping under these risk conditions.
- Several physiologic responses mediated by the ANS are depressed when infants sleep on their stomachs. These include reactivity to noise, sudden decreases in blood pressure, and tactile stimulation. There is also a reduction in heart rate control in the prone position, as well as decreased movement, less waking, longer periods of deep sleep, and higher arousal thresholds.
- The heart rate response following postural adjustment (tilt) is a reliable measure of the competence of neural mechanisms to process and respond to sudden changes in blood pressure. During the vulnerable period for SIDS, infants have diminished responses to this challenge.
- Epidemiologic studies have reaffirmed a strong relationship between amounts of cigarette smoking during pregnancy and SIDS. The development of neural substrates for autonomic control is susceptible to the known toxic effects of exposure to alcohol and smoking during gestation. Basic research has pointed to a relationship between nicotine exposure and autonomic function during the fetal period.

Smoking has also been shown to lead to low birthweight, alterations in baseline heart rate and blood pressure, and blunted responses to hypoxia, which are characteristics of many SIDS victims.

- Recent psychobiological research findings suggest that important continuities exist in fetal and infant neurobehavior. Individual differences in patterns of fetal heart rate, movement, and sleep-state organization predict similar patterns in newborns and older infants.

Goals and Objectives

Goal: Elucidate the role of the continuity of fetal and infant autonomic development and dysfunction in the etiology of sudden unexplained deaths.

- **Objective:** Study the longitudinal development of fetal-to-infant cardiorespiratory and cardiovascular control. In addition to illuminating the origin and nature of the pathogenic process, these studies may help to identify the most vulnerable infants before they enter the period of greatest risk.
- **Objective:** Investigate the role of prenatal environmental factors (e.g., smoking, nutrition, toxins) that function to degrade or improve the capability of the ANS to respond to potentially life-threatening challenges.
- **Objective:** Initiate multidisciplinary approaches to investigate interactive effects of smoking with other prenatal risk factors, such as alcohol, stress, and fetal nutrition.
- **Objective:** Extend investigations of developmental neurobehavioral deficits to other clinical entities, such as fetal demise, stillbirth, or childhood syncope (fainting), which may share similar risk profiles as well as central nervous system (CNS) deficits with SIDS.

- **Objective:** Investigate the contribution of preterm birth to autonomic dysfunction and SIDS pathogenesis.

Goal: Investigate the repertoire of responses to life-threatening challenges in the infant's environment.

- **Objective:** Continue to study the developmental changes in control of breathing as well as the compensatory behavioral changes required under conditions of reduced oxygen and increased carbon dioxide (rebreathing of expired air).
- **Objective:** Evaluate mechanisms required to mount adequate cardiovascular responses to hypotensive challenges during the vulnerable period for SIDS.
- **Objective:** Understand the mechanisms underlying a possible shock-like response leading to sudden death in infants. Include studies of related autonomic disorders, such as Congenital Central Hypoventilation Syndrome, which is characterized by a number of physiologic deficits similar to those of infants who later succumb to SIDS, including lower heart rate variability and cardiorespiratory responses to blood pressure challenges.
- **Objective:** Investigate the long-term effects of postnatal environmental factors (e.g., sleep position, thermal stress) on the development and function of the ANS.

Infant Care and the Sleep Environment

Background

- Depending on the study, between 10 and 60 percent of SIDS infants are found with their face, head, or entire body covered by a blanket, comforter, pillow, or other form of bedding. Between 25 and 50 percent

are found dead facedown in the bedding. Laboratory studies have shown that these situations can cause fatal asphyxia and/or dangerous overheating; these are presumed to be the lethal mechanisms underlying the increased risk of sudden death that is associated with a prone sleeping position.

- Epidemiologic studies have shown that soft bedding, such as sheep skins, pillows, quilts, or soft mattresses of several types, are risk factors for SIDS, particularly in infants who sleep prone.
- "Accidental suffocation" is a preventable cause of death in infancy that occurs somewhat less frequently than SIDS: 0.1-0.5/1,000 live births affected by accidental suffocation versus 0.7/1,000 live births affected by SIDS. Accidental suffocation is difficult to distinguish from SIDS because postmortem findings may be similar and the age of peak risk overlaps between the two. The diagnosis often depends on an estimation of whether an infant would have been physically capable of escaping entrapment. Since this is often a subjective assessment, such judgments tend to further obscure differences between SIDS and accidental suffocation cases.
- Use of adult furniture, such as sofas or adult beds, is a risk factor for both SIDS and accidental suffocation. The potential for entrapment created by crevices in bedding, the presence of bed partners, and the lack of protective barriers may, in part, underlie this risk.
- Infants who are unaccustomed to sleeping on their stomachs are at risk for SIDS when they are put down prone or turn onto their stomachs spontaneously. A high percentage of such infants are found facedown at death. Studies suggest that head turning to avoid airway obstruction or rebreathing is a learned behavior.

- Some studies have shown that if an infant is sleeping in the same room with the mother but in a separate bed space (crib or bassinet), the risk for SIDS is lower in comparison with putting the infant to sleep in a separate room.
- Mothers and infants sleeping together on a shared surface (e.g. bed, mat, floor) is widely practiced throughout the world. Factors that increase the risk for SIDS or accidental suffocation under bed-sharing conditions include characteristics of the bed or bedding that create a potential for falling to the floor or entrapment, maternal cigarette smoking, maternal use of alcohol in moderate to large amounts, excessive maternal fatigue, and bed-sharing with individuals other than the mother.
- Intentional suffocation is often impossible to distinguish from SIDS and may be the true diagnosis in no more than 5 percent of SIDS cases.

Goals and Objectives

Goal: Elucidate the infant's neural capacity to avoid risky sleeping situations.

- **Objective:** Develop reliable examination techniques to determine an infant's capacity to arouse, and avoid facedown or other potentially asphyxiating situations.
- **Objective:** Investigate thermal control in infants and potential thermal stressors.
- **Objective:** Consider collaborations with other Federal agencies to develop practical standards for assessing bedding softness, rebreathing, and thermal insulation characteristics (togs) that can be interpreted readily by industry and infant caregivers.
- **Objective:** Determine whether "tummy time" or other types of experience improve an infant's ability to avoid potentially asphyxiating situations (e.g., lying facedown with the head covered).
- **Objective:** Perform studies of infant behaviors and neurologic development predisposing to entrapment and to the ability to evade or escape entrapment in order to improve the design of safe child furnishings.

Goal: Elucidate traditional and new methods of child care and the use of bedding with the potential to reduce the risk of sudden death.

- **Objective:** Investigate types of bedding that provide adequate insulation without rebreathing or thermal-stress risks.
- **Objective:** Investigate methods of child care that might minimize the risk of infants spontaneously turning to the prone position, covering their heads, or suffering from "wedging" deaths during sleep. Examples include the use of the Dutch sleeping sack, Polynesian hammocks, modern car seats, and Native American cradle boards.

Goal: Elucidate differences between SIDS and accidental suffocation.

- **Objective:** Develop new forensic tools that will assist in distinguishing SIDS from accidental and/or intentional suffocation.
- **Objective:** Perform forensic studies to clarify and standardize the diagnoses of SIDS, accidental suffocation, positional asphyxia, intentional suffocation, overlaying, and cause of death undetermined.
- **Objective:** Perform epidemiologic studies of SIDS, accidental suffocation, and cause of death undetermined with particular emphasis on child care practices (e.g., room sharing, bed sharing).

Goal: Elucidate the role of child care practices prevalent in day care in relationship to SIDS.

- **Objective:** Study sudden unexpected deaths that occur while infants are being cared for by day-care providers (licensed and unlicensed) in order to identify specific risk factors that might be increased in these settings. A case-controlled setting might uncover novel risk factors, such as the timing or frequency of infant observation.

Infectious Disease and Immunity

Background

- Several factors suggest a role for infection in the pathogenesis of SIDS: (1) the increased occurrence of SIDS in winter and spring when increased infectious respiratory and gastrointestinal diseases are seen in infants, (2) the peak occurrence of SIDS with the waning occurrence of maternal immunity and first exposures to many pathogens, and (3) the association of SIDS deaths with recent upper-respiratory-tract and gastrointestinal infections.
- A role for infection in SIDS is also suggested by autopsy findings of mild inflammatory changes at a variety of levels of the respiratory tract and elevations of specific inflammatory cytokines, chemokines, and/or pathogen- or toxin-specific antibodies in a variety of body fluids or tissues in SIDS babies.
- The increased risk for SIDS associated with lower socioeconomic status may relate to an increased exposure to infectious agents at a younger age.

- The decreased risk for SIDS associated with breastfeeding may relate to immune factors passed to the infant through breast milk.
- Over the past 30 years, multiple attempts have been made to *directly* link pathogens (such as respiratory syncytial virus, enteroviruses, *Staphylococcus aureus*, and *Clostridia* species) to SIDS, but numerous methodological and technical problems have characterized these studies, and they all remain inconclusive. Their weaknesses include small sample size and the lack of appropriate controls. Many of the infectious agents are ubiquitous, with only loose associations with SIDS. No single pathogen has been proven to cause SIDS or a subset of SIDS.
- Proposed potential mechanisms for the role of infection in SIDS include partial airway obstruction by respiratory tract infection, which may lead to disorders of sleep arousal, sleep deprivation stress, or apnea, and complex theories of inflammation (i.e., cytokine-induced changes affecting the central nervous system). The studies performed to date often attempt to implicate infectious agents working in conjunction with other cofactors, such as prenatal nicotine exposure and sleep position. Direct evidence for these theories is lacking.

Goals and Objectives

Goal: Elucidate immunologic/inflammatory responses influenced by a variety of infectious agents and their interactions with the host, the developing infant.

- **Objective:** Determine the common pathways of the inflammatory response incited by a wide variety of infectious agents, and the mechanisms that may affect other known developmental physiological factors, such as sleep patterns and arousal.

- **Objective:** Determine developmental aspects of the immune system that may alter the inflammatory response in the SIDS age range.
- **Objective:** Determine novel pathophysiologic mechanisms of particular pathogenic agents that involve one or more homeostatic systems and result in sudden death in infancy.

Goal: Examine the contribution of infectious agents in the context of carefully designed large-scale, prospective epidemiologic (case control) studies of SIDS.

- **Objective:** Analyze a wide variety of infectious agents, looking for common pathways and interactions with known SIDS risk factors and current etiologic hypotheses. Avoid bias towards identifying a role for a specific pathogen unless a particularly unique mechanism can be elucidated.
- **Objective:** Delineate the natural history (rates of infection and colonization) of potentially contributing infectious agents in the infant population, and their interactions with the host immune system (inflammatory response).

Genetics

Background

- Studies to determine whether SIDS is hereditary show that SIDS does not behave like a classical genetic disease with a 25- to 50-percent risk of occurrence among siblings. There is controversy over whether SIDS recurs in families, but if it does, the risk for subsequent siblings is probably less than 0.5 percent.
- Since SIDS is a syndrome, genetic factors will likely be of variable importance, playing a small role in some cases and being of major importance in others.

As environmental risk factors, such as sleep position, are identified and minimized through public education campaigns, genetic causes of SIDS may play an increasingly more decisive role in the remaining cases.

- Known genetic disorders of metabolism likely account for up to 5 percent of SIDS cases. Other genetic diseases, such as prolonged QT syndrome, may contribute to SIDS in a small percentage of cases.
- Increasing knowledge of SIDS-associated abnormalities, such as developmental brainstem anomalies or association with upper respiratory infections, is suggesting possible genetic risk factors (i.e., “susceptibility genes”) that may predispose an infant to SIDS.
- Genetic factors or their interactions with environmental factors may account in part for the variations in SIDS incidence observed across subgroups of the population. The incidence of SIDS varies widely among racial and ethnic groups in the United States, yet it is not clear to what extent genetic factors may contribute to this variation.
- The successful completion of a complete DNA sequence of the human genome is providing research opportunities to identify genes that may influence an infant’s risk for SIDS.
- Knowledge of the structure and sequence of all human genes has made it possible to screen rapidly and easily any potential SIDS-related gene for mutations.
- The development of rapid and efficient methods for identifying natural variations in the human genome is making genomewide searches for SIDS-susceptibility genes possible.



- Identification of the complete repertoire of human genes and the development of high-throughput microarray-based methods to measure gene expression have made it possible to examine the complete pattern of gene expression in the tissues of SIDS victims.

Goals and Objectives

Goal: Elucidate the role of gene-environment interactions in SIDS and related disorders.

- **Objective:** Conduct genetic epidemiologic studies to characterize the distribution of genetic traits and outcomes related to SIDS in populations or families to include disorders of fetal development, autonomic disorders, stillbirths, and other infant and childhood deaths.
- **Objective:** Conduct epidemiologic studies to characterize the determinants of the distribution of genetic traits and their relation to disease in populations or families.
- **Goal:** Evaluate potential "SIDS genes" through mutation searches and association studies of potential candidate genes to be selected based on their known relationships to physiologic processes relevant to SIDS.
- **Objective:** Evaluate the incidence of known genetic disorders, such as metabolic diseases of fatty acid metabolism or inherited cardiac arrhythmias, including long-QT syndrome, among cases of SIDS. Encourage multidisciplinary studies that utilize genetic, biochemical, and pathologic approaches to identify and characterize SIDS cases attributable to single-gene disorders.
- **Objective:** Identify and evaluate potential associations between genotypic polymorphisms in candidate SIDS-susceptibility genes and SIDS. Candidates will be chosen based on knowledge of SIDS epidemiologic risk factors, such as recent infection (e.g., cytokines, complement genes) and overheating (e.g., heat shock genes) as well as neuropathologic studies implicating abnormal brainstem development and cranial dysmorphism (e.g., homeobox and other developmental genes).
- **Goal:** Identify SIDS-susceptibility genes through large-scale genomewide association studies in clearly defined high- and low-risk populations.
- **Objective:** Collaborate with other Institutes to encourage the development of methods for high-throughput genotyping methods for the analysis of functional genetic polymorphisms and silent single nucleotide polymorphisms (SNPs).

- **Objective:** Support one or several large-scale genetic association studies using high-density maps of functional and nonfunctional SNPs to identify genes and regions associated with increased susceptibility to SIDS.
 - **Objective:** Conduct followup studies to determine the role(s) played by these genes in normal development and/or homeostasis, and identify particular environmental risk cofactors that may act in concert with each susceptibility gene.
- Goal:** Understand the “vulnerable” physiologic state of dysfunctional tissues associated with SIDS and related deaths in order to elucidate interactions with known environmental risk factors.
- **Objective:** Support research utilizing the latest advances in microarray-based gene expression studies to characterize global patterns of gene expression in the tissues of SIDS victims and normal controls. Anatomic areas to be examined will be selected on the basis of current anatomic studies implicating abnormal development of specific regions.
 - **Objective:** Support second-generation proteomic studies of SIDS and control tissues to confirm and extend the results of the gene expression studies.
 - **Objective:** Facilitate multidisciplinary collaborations to correlate patterns of gene and protein expression with epidemiologic, clinical, physiologic, and pathologic data for a more complete understanding of the role of gene expression in the disease process.

Sudden and Unexpected Death in Childhood

Background

- About 175 children between the ages of 1 and 4 die in the United States each year from unknown causes, a substantial fraction of these are sudden and unexpected.
- Sudden and unexpected death in childhood, although rare, is devastating.

Goals and Objectives

Goal: Understand the underlying causes and mechanisms of sudden unexpected death in children between 1 and 4 years and their relationship to SIDS.

- **Objective:** Evaluate trends in the incidence of sudden and unexpected childhood deaths in the United States and abroad from 1985 to the present.
- **Objective:** Evaluate the relationship between these deaths and SIDS by investigating the epidemiology, genetics, and pathology of these cases.
- **Objective:** Evaluate the contribution of inborn errors of metabolism and cardiac arrhythmias to the cause of death in these cases.

Infrastructure: DNA and Tissue Banks

Background

- Developmental banks provide an opportunity for investigators to obtain samples from victims of rare disorders and deceased normal controls, which are equally rare.
- Establishing banks permits adequate sample sizes to be collected more quickly than any individual researcher is capable of doing alone.
- Banks follow standard clinical, pathologic, and biochemical protocols, which facilitate uniformity in the quality of the research material and ensure the collection of necessary case information.

Goals and Objectives

Goal: Continue the NICHD-sponsored “Brain and Tissue Banks for Developmental Disorders” program, which banks samples of normal and diseased brain tissues from fetal life through adolescence. These brain banks make clinicopathologic data available for correlation with brain findings and have proven to be useful for SIDS research.

- **Objective:** These banks should have provisions to permit different investigators working on different parts of the same brain to compare their findings; similarly, they should facilitate the correlation of investigators’ systemic findings in different organ systems of the body. In this way, all the findings

relating to one case could be integrated, and a more complete clinicopathologic picture would emerge.

- **Objective:** Encourage the collection and annotation of pathologic specimens for biochemical studies of gene and protein expression, and infectious agents. Support the development of a centralized database listing availability and clinical and pathologic characteristics of specimens from critical tissues of SIDS victims, such as the brainstem, liver, bone marrow, and blood.

Goal: Facilitate future genetic studies of SIDS through the development of DNA and tissue banks for specimens from SIDS victims and relatives, including full and half-siblings.

- **Objective:** Support the development of a comprehensive DNA bank to include specimens from SIDS victims, their parents, and siblings. DNA samples should be linked to phenotypic data collected through new and existing NICHD-supported clinical studies. Coded DNA samples should be made available to qualified investigators for genetic studies of candidate SIDS-related genes and genomewide searches for genetic risk factors for SIDS. Prospective informed consent will allow recontact of families for appropriate followup studies.
- **Objective:** Consider utilizing nontraditional sources for the collection of biologic specimens, such as banked blood spots, or specimens banked from past or ongoing epidemiologic studies of pregnant women and their offspring.

Prognostics and Diagnostics

Statement of the Problem

Despite our knowledge of selected SIDS risk factors, no population characteristics have been identified that provide sufficient predictive value to permit the prospective identification of an individual infant at risk for SIDS. Although geographic and socioeconomic disparities exist, most infants who die from SIDS do not fall into any well-defined risk group. Although the majority of SIDS deaths may be associated with a single underlying mechanism, infants currently considered to have died from SIDS include deaths from a number of distinct causes. Therefore, the sensitivity of any screening test based on one mechanism of death would be limited since it would not be expected to identify infants at risk of death from alternative causes. In addition, the specificity of screening may be limited since it is likely that only a fraction of those infants who have an underlying vulnerability for a particular cause of SIDS will go on to die.

Based on the studies available to date, it may be unrealistic to expect an individual screening test to have a sensitivity surpassing 50 percent or a specificity greater than 97 percent. If such a screening test were implemented, based on the current SIDS rate in the United States of 0.7 per 1,000, the proportion of SIDS deaths even among infants testing positive would be approximately 1 percent. The low rate of occurrence of SIDS makes it particularly difficult to perform the prospective studies needed to validate screening tools. However, the development of methods of identifying infants at higher risk of SIDS would greatly enhance

research efforts. Following an initial screening, which would have to test large numbers of infants efficiently in order to be useful, those with a high risk of SIDS (e.g., 1 percent or greater) would then become candidates for more intensive study.

Without a means of identifying infants or groups of infants at high risk for SIDS, studies that are invasive, expensive, and/or time consuming are not practical. For example, studies that have used home cardiorespiratory monitoring have been able to shed light only on the nature of the cardiorespiratory events experienced. Home monitoring as currently performed is not a practical approach for the study of a population



sufficiently large enough to draw meaningful conclusions with regard to SIDS. However, data gathered from infants who succumbed while on monitors have helped shape investigations into certain physiologic deficits that may lead to SIDS.

It is likely that continued research into the basic mechanisms underlying SIDS will nourish developments in prognostics and diagnostics. For example, neuropathologic studies of SIDS victims point to likely candidates for markers of autonomic deficits. In addition, investigations of possible genetic contributions may ultimately lead to prenatal and neonatal screening procedures for diseases and disorders associated with SIDS.

Continued epidemiologic investigation of genetic and environmental factors, in concert with investigations of developmental physiology and neuropathology associated with SIDS, will provide far greater specificity than possible today to define risk groups. Studying infants from high-risk groups may then offer an opportunity to identify potential markers or profiles that may be associated with an individual's vulnerability for SIDS. Preventative or therapeutic strategies could then be designed based on rigorous diagnostic criteria and could be targeted at the specific underlying deficits found in high-risk populations or individuals.

Background

- Prospective studies of large numbers of infants have identified characteristics that are more common in newborns who subsequently died of SIDS compared with living newborns, including higher heart rates, reduced heart rate variability associated with respiration, increased variability of breathing during quiet sleep, abnormalities in the beat-to-beat dynamics of cardiac control, prolonged QT intervals, and abnormal acoustical cry characteristics.
- Prospective studies replicating these findings and evaluating the relationship of each of these variables to one another have not been done.
- Alternative linear and nonlinear methods of measuring heart rate variability have been proposed as markers of autonomic instability. Among linear analyses, time and frequency domain approaches are used to exploit heart rate rhythms as a means of assessing maturation of cardiac and ANS control during the fetal and early infant period. Since decreased heart rate variability under different conditions—e.g., during deep sleep or in the prone position—may be a sign of autonomic impairment, this measure may provide a means of very early assessment of risk for autonomic dysfunction during the late fetal and neonatal periods.
- Nonlinear analyses of instantaneous heart interval have been useful in identifying adults with cardiac disease who are at imminent risk of heart attack. These alternative approaches for evaluating heart rate variability may provide an opportunity to better quantify disturbances in heart rate variability that have been found using more conventional approaches to study SIDS.
- The heart rate response following postural adjustment (tilt) is a reliable measure of the competence of neural mechanisms to process and respond to sudden changes in blood pressure. The degree of vasoconstriction in response to tilt is also emerging as a promising measure of ANS development. During the vulnerable period for SIDS, infants have diminished responses to this type of challenge.
- Studies that have utilized home monitoring have been able to shed light only on the nature of cardiorespiratory events experienced. Home monitoring as currently performed is not a

practical approach for the study of a sufficiently large population to draw meaningful conclusions with regard to SIDS.

Goals and Objectives

Goal: Develop technology for assessing SIDS risk factors in large populations.

- **Objective:** Utilizing advances in technology, including digital storage capacity and signal processing techniques, develop systems capable of efficiently processing physiologic and other signals that have been or may be described as associated with increased risk for SIDS, including heart rate and blood pressure coherence and variability, QT interval, breathing rate variability, and cry acoustics.

Goal: Identify screening tests for SIDS capable of identifying infants at high risk of SIDS in whom indepth prospective studies would be feasible.

- **Objective:** Encourage and support research that would utilize experimental designs, such as randomized clinical or community trials, to evaluate screening tools empirically. This would include, but not be limited to, measurement issues such as sensitivity, specificity, and predictive value of existing or promising new screening tools. Trials that are sensitive and responsive to the characteristics of the target population (such as racial/ethnic and sociocultural factors) should be especially encouraged.
- **Objective:** Based on existing data sets and new studies, assess developmental patterns in characteristics that have been reported as associated with increased risk for SIDS.

- **Objective:** Assess the interrater reliability and validity of proposed infant assessments, and develop and disseminate guidelines for the appropriate performance of proposed infant assessment techniques.

Goal: Develop assessments derived from the integration of postmortem findings with physiologic studies.

- **Objective:** Support research for the development of noninvasive probes of function known to be associated with deficits in brainstem areas, e.g., thermoregulation, sensory and motor activity, control of breathing, sleep arousal, and cardiovascular reactivity.

Goal: Encourage methodologies for assessments of developmental neurobehavioral deficits of clinical entities possibly related to SIDS, such as fetal demise and childhood syncope (fainting), which may share similar risk profiles as well as central nervous system deficits.

- **Objective:** Support research for the development of tools to assess the competencies required to mount adequate cardiovascular responses to hypotensive challenges during the vulnerable period for SIDS.
- **Objective:** Quantify continuities in fetal-to-infant cardiorespiratory control in order to identify the most vulnerable infants before they enter the period of greatest risk.
- **Objective:** Develop noninvasive techniques to assess the maturation of compensatory mechanisms in high-risk groups, including gasping ability, the ability to arouse to a safer state, and somatomotor adjustments needed to respond to challenges during the vulnerable period.



FROM CELLS TO SELVES

- **Objective:** Perform studies to elucidate underlying physiologic vulnerabilities in infants of mothers who smoked during pregnancy and in low-birthweight infants, both of which are at increased risk of SIDS according to epidemiologic studies.

Goal: Evaluate prenatal and neonatal screening procedures for diseases and disorders associated with SIDS.

- **Objective:** Development of improved methods for the early detection of fatty acid oxidation disorders is needed to allow for interventions to prevent metabolic crises that can lead to sudden infant deaths.
- Encourage development and evaluation of high-throughput, high-sensitivity screening tests, e.g., tandem mass spectroscopy, to detect fatty acid oxidation disorders as a group.
- Support development and evaluation of efficient and sensitive genetic mutation detection methods for each of the fatty acid oxidation pathway genes associated with SIDS.
- **Objective:** Evaluate the contribution of prolonged QT syndrome and associated genotypes to sudden deaths in infancy.

Preventive Strategies

Statement of the Problem

When we think of preventing disease, the classic example is infectious disease. In this case, vaccination and public health strategies to reduce the exposure to an infectious agent protect individuals from contracting the infection. However, most human diseases and disorders result from multiple interacting factors that include individuals' genetic makeup, their lifestyles, and the physical and cultural environment in which they live. Thus, when we are concerned with prevention strategies, we must understand the extent to which particular factors in the population increase or decrease the probability of disease development. Those factors deemed to most strongly influence the degree of risk are targeted for intervention.

In the section on Etiology and Pathogenesis, we presented a triple-risk model for SIDS. According to this model, if we can eliminate prenatal factors that increase the risk of developmental abnormalities in the fetus, we may reduce the likelihood of a SIDS death. If we can positively alter the developmental trajectory during the critical period, we may also reduce the likelihood of a SIDS event. Removing environmental risk factors in the critical period that are hazardous to the infant may also be effective in reducing risk. Placing an infant on the back to sleep is an excellent example of reducing a major environmental risk factor.

The more we know about how risk factors contribute to SIDS pathogenesis, the more confident we can be that an infant will not succumb to SIDS. SIDS occurs during the early months of an infant's life, when he or she is

extremely dependent on the caregiver. It is a time of adjustment and learning for the infant and the caregiver, as each gets to know the other and the baby becomes familiar with the extrauterine environment. The early months are also a time of rapid growth and development, with changing nutritional and sleep requirements.

To prepare for these changes, the baby needs a healthy start during the prenatal period. What are the requirements for normal development? What factors increase the likelihood that the developmental process will go awry? How can we reduce the risk that they might? Our knowledge of human development in fetal life and early infancy is still quite limited. Although research on SIDS risk factors has identified prenatal and postnatal environmental characteristics and care practices that are critical to healthy outcomes, more research is needed.

Historically, women are the primary decision-makers for family health care and the major caregivers for infants, children, and elderly relatives. In modern times, additional demands and stresses occur as more and more women work outside the home as well as within it. Furthermore, the proportion of single-parent households headed by women continues to increase. Therefore, preventive strategies targeting SIDS must, of necessity, also address issues of women's health. Women's health during the periconceptional, prenatal, and postnatal periods profoundly influences the health of the developing fetus and the newborn.

Since we cannot presently identify those individual infants who are predisposed to SIDS, any intervention aimed at reducing the risk of SIDS must be designed for

the entire population of babies and/or pregnant women. In the United States, our society is heterogeneous. Subpopulations can be defined by many criteria, such as geography, race, ethnicity, or socioeconomic characteristics. We have learned that the definition of a population will influence the development of the risk profile, the nature of the intervention, and the way in which an intervention is implemented. During the next 5 years, efforts to improve the effectiveness of SIDS risk-reduction interventions will need to harness the strengths that lie within communities and cultures.



Research

Background

- Case-control studies have identified the following maternal characteristics as increasing the risk for SIDS: maternal age under 20 at first pregnancy, a short interval between pregnancies, late or no prenatal care, placental abnormalities, and urinary tract infection during pregnancy.
- Maternal cigarette smoking during pregnancy increases the risk of SIDS about threefold, independent of the birthweight of the baby. The risk increases with the number of cigarettes smoked per day.
- Some studies have shown that cigarette smoke in the baby's environment after birth also increases SIDS risk. The risk has been shown to increase with either the number of cigarettes smoked by the parents or the number of hours the infant spends in the presence of smokers. However, it is difficult to separate the contribution of prenatal and postnatal smoke exposure.
- Maternal drug abuse during pregnancy increases the risk for SIDS, and preliminary findings suggest that maternal binge drinking also increases risk.
- Low birthweight and prematurity increase the risk of SIDS; the risk increases with decreasing birthweight and gestational age.
- If an infant is placed to sleep in the prone position, the risk for SIDS is increased threefold to ninefold. Most studies have found that infants placed to sleep on their sides are at twofold increased risk compared with those placed on their backs.

- If an infant is placed to sleep on soft bedding, including blankets, pillows, sofas, and adult bed mattresses, the risk for SIDS increases. The use of a quilt increases the risk of SIDS for infants placed to sleep on their backs. Many SIDS infants are found dead with the head or face covered with bedding.
- The presence of recent viral, respiratory, or gastrointestinal illnesses enhances the risk for an infant placed to sleep on the stomach or for an infant who is over bundled (i.e., covered by more clothes and blankets than necessary for the room temperature).

- Although sharing a room with the parents may be protective, sharing a bed appears to increase risk under certain conditions. These include maternal smoking, recent maternal alcohol consumption, and parental fatigue, as well as the use of a quilt to cover the infant and the infant sleeping with individuals other than parents.
- Some studies have found that infants who are breastfed are less likely to die from SIDS. However, other studies have failed to find a protective effect after other factors have been taken into account. Infants who are bottle-fed are not at increased risk for SIDS.
- Several studies have shown that infants who use pacifiers are at decreased risk of SIDS.
- Preliminary results from a study of infant mortality among Northern Plains Indians demonstrate that home visits by public health nursing personnel have a strong protective effect on infants at risk of SIDS.

Goals and Objectives

Goal: Continue to elucidate environmental risk factors and the timing of exposures that are amenable to public health action.

- **Objective:** Foster multidisciplinary research focusing on known risk factors for SIDS (e.g., smaller birth size, earlier maternal age, multiple births) and relatively unstudied environmental agents, including chemicals (e.g., pesticides, heavy metals, persistent organochlorines) and physical agents (e.g., temperature, air particulate matter) in order to delineate the role of each in the pathophysiology of SIDS. Certain environmental agents have been linked to reduced birth size and developmental delays in infants, both of which are associated with an increased risk of SIDS.



- **Objective:** Support research to determine the period of fetal or infant vulnerability or susceptibility to environmental agents. Research designs that support the use of statistical techniques to assess methodological issues such as the timing and duration of exposures (before, during, and after pregnancy) are needed.

Goal: Continue to examine the role of maternal health before and after birth in influencing SIDS risk and the risk for unexplained stillbirths.

- **Objective:** Foster multidisciplinary research to investigate the role of abnormal placental function in SIDS risk prospectively.
- **Objective:** Further investigate the association of genitourinary tract infections with increased SIDS risk by examining the pathogens, timing of infection, and relationship of infection to preterm births, potential placental or fetal pathologies, and maternal age.
- **Objective:** Examine the role of maternal chronic diseases such as asthma and diabetes in influencing SIDS risk.
- **Objective:** Investigate the contribution of health programs designed to improve maternal and infant health—e.g., home visits by public health nurses before and after birth—to decreases in SIDS risk.
- **Objective:** Further investigate the effects of prenatal and postnatal cigarette smoke exposure on SIDS risk in order to understand the pathogenic mechanisms involved and to refine public health messages.
- **Objective:** Support multidisciplinary studies elucidating the contribution of prenatal and postnatal alcohol consumption to SIDS risk, including the timing

and pattern of alcohol use, as well as determinants of maternal drinking behaviors.

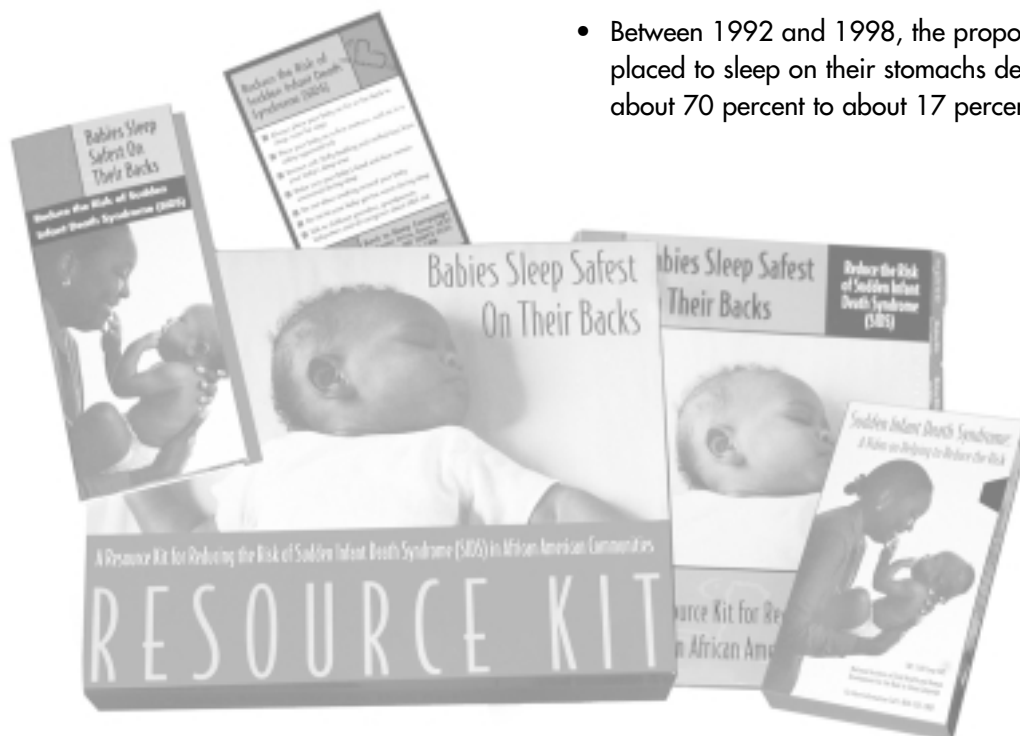
Goal: Encourage research that simultaneously addresses a multitude of risk factors for SIDS and related outcomes in order to determine the nature and magnitude of known (e.g., sleep position and bed sharing) and potential interactions and to develop a rank ordering of risk factors amenable to public health intervention. This avenue of research should consider genetic, lifestyle, behavioral, and environmental factors in order to model infants' postnatal lives more accurately.

- **Objective:** Further examine the interactions among characteristics of the sleep environment, including sleep position, bedding, environmental temperature, infant clothing, bed sharing, and room sharing.
- **Objective:** Describe patterns of bed sharing and elucidate the risk of SIDS and accidental suffocation under a variety of environmental conditions, including phenomena such as overlay.
 - Investigate the role of infant characteristics (e.g., age, arousal characteristics, and protective behaviors) and maternal characteristics (e.g., postnatal smoking and alcohol consumption) in determining the levels of risk associated with bed sharing.
- **Objective:** Determine the role of pacifiers in reducing SIDS risk and assess the risks versus benefits in order to formulate recommendations regarding pacifier use.
- **Objective:** Continue to monitor the influence of prevention messages on health outcomes in order to identify unintended consequences, both positive and negative.

Interventions

Background

- In 1992, the American Academy of Pediatrics (AAP) released a recommendation that healthy infants should be placed to sleep on their sides or backs to reduce the risk of SIDS.
- In 1994, the national public education campaign, *Back to Sleep*, was launched by a coalition consisting of the U.S. Public Health Service, the AAP, the SIDS Alliance, and the Association of SIDS and Infant Mortality Programs. The campaign recommended that infants be placed on their backs or sides to sleep to reduce SIDS risk.
- The campaign also recommended that babies should be placed to sleep on a firm mattress. Blankets and comforters should not be placed under the baby, and pillows and stuffed toys should not be placed in the crib.
- Secondary campaign messages included maintaining a “smoke-free” zone around the baby before and after birth, and regular prenatal and well-baby care.
- The campaign disseminated information to hospital nurseries, physicians, and licensed day care centers and initiated public media campaigns nationwide.
- In 1996, the AAP and the *Back to Sleep* campaign revised the basic recommendation to state that the back is the preferred sleeping position and safer than sleeping on the side.
- In 1999, in collaboration with the Consumer Product Safety Commission, a safety alert was released to remove all soft bedding, including quilts and comforters, from cribs.
- Between 1992 and 1998, the proportion of infants placed to sleep on their stomachs declined from about 70 percent to about 17 percent.



- About one-third of caregivers who placed infants on their sides or backs at 1 month of age switched to placing infants on their stomachs by 3 months of age.
- By 1998, almost 95 percent of the survey population reported receiving a recommendation encouraging back or side position. Of those who placed their babies on their stomachs, 86 percent had only received a recommendation for back or side sleeping positions. The majority said the reason for choosing the riskier position was that the baby liked it better or slept better that way.
- Between 1992 and 1998, the SIDS rate declined by about 40 percent, from 1.2/1,000 live births to 0.72/1,000 live births.
- The prevalence of soft bedding being placed under the baby has not decreased since 1992.

Goals and Objectives

Goal: Actively work with communities to obtain information on cultural variances with regard to the *Back to Sleep* campaign messages. Obtain feedback and advice from communities on ways to address cultural variances effectively and to identify ways to refine campaign messages in light of cultural differences.

- **Objective:** Conduct research to identify social, cultural, and behavioral factors that influence SIDS risk reduction.
- **Objective:** Target barriers that may exist in various communities. Design interventions and education programs about safe sleep practices for infants that take into account the influence of such barriers.
- **Objective:** Develop materials with tailored messages to address specific actions in order to reduce the risk of SIDS. Such messages should include concrete statistical information describing

relative degrees of risk and ensure clarity in conveying information on SIDS. Conduct focus groups to test whether messages are appropriate for specific populations and subpopulations.

Goal: Promote research to broaden the understanding of cultural variations existing among communities with high rates of infant deaths. Such variations should also be studied among communities where risk-reduction messages may not have penetrated, such as the child-care provider community.

- **Objective:** Encourage studies aimed at identifying relationships between risk factors and existing cultural practices. Research should include strategies to enhance our understanding of how the reception of risk-reduction messages is influenced by different cultural practices.
- **Objective:** Foster studies to explore methods for effectively crafting culturally appropriate messages.



Measures should be studied to disseminate culturally appropriate messages that identify effective processes to tailor communications that target diverse groups.

- **Objective:** Encourage research to study long-term effects of risk-reduction messages on populations in the context of varying cultural practices.
- **Objective:** Assure methods are implemented to evaluate risk-reduction communications and their effects on cultural groups.

Goal: Ensure that the *Back to Sleep* campaign messages are sustained and remain consistent throughout all outreach activities and initiatives. Actively seek out other agencies and organizations and collaborate with them to assist with continued campaign efforts.

- **Objective:** Ensure that the *Back to Sleep* campaign messages are updated to reflect current SIDS research. Keep campaign partners informed of SIDS research and changes in campaign messages.
- **Objective:** Conduct process evaluation to assess efficacy of ongoing campaign activities. Share information and findings with the collaborative partners to maintain the campaign's cohesiveness.
- **Objective:** Enhance the NICHD's partnerships with agencies, community leaders, and organizations to communicate *Back to Sleep* messages in the communities these entities serve.
- **Objective:** Develop and implement strategies with partner organizations and the Consumer Product Safety Commission to decrease the use of soft bedding in the infant sleep environment.

Goal: Develop and implement interventions that are favorable to women's health.

- **Objective:** Education and prevention activities and services should be offered to people where their daily activities take place, such as Women's Wellness clinics, well-child clinics, and school prevention programs. The staff providing such services should work closely with school nurses, where available. Often, mobile clinics and flexible clinic hours are necessary to accommodate working mothers and their families. Human and financial resources need to be identified and coordinated to improve the health status of women and their families.
- **Objective:** Collaborate with other programs inside and outside the Institute to promote smoking cessation before and after birth.

Infrastructure

Background

- Perinatal infant mortality review is not conducted consistently throughout the country. Some local jurisdictions lack review teams.
- Perinatal infant mortality review under uniform conditions provides information on trends and patterns of fetal and child deaths; when coupled with standardized data collection, it can inform about public health policy and guide research and prevention activities.
- Perinatal infant mortality review provides a forum for the uniform diagnosis of unexpected and/or preventable deaths, and the expedited follow-up of cases.

Goals and Objectives

Goal: Improve the diagnosis and surveillance of sudden unexpected fetal and infant deaths to optimize the development and monitoring of prevention efforts.

- **Objective:** Work with other agencies at the national and local levels to provide uniform guidelines and training for perinatal infant mortality review personnel that take the limited resources of many small or rural communities into account.
 - Educate health professionals and involved community members in the conduct of the reviews, with guidelines describing methods of data collection, analysis, review, and follow-up. Emphasize multiagency efforts that include infant and toddler health as well as high-risk pregnancies.
 - Develop expanded information systems to facilitate comprehensive reviews.

- **Objective:** Continue to work with other agencies and nongovernmental organizations to improve the diagnosis of sudden unexpected infant deaths through coroner mentoring programs and health-professional education.
- **Objective:** Review the knowledge accrued over the next 5 years to determine whether the standard SIDS definition should be revised to increase the specificity of diagnosis, including possibly changing the age range.

Goal: Continue to strengthen the *Back to Sleep* Coalition.

Health Disparities

Statement of the Problem

Eliminating the disparities in SIDS rates among minority communities is one of the most important and challenging problems facing SIDS researchers in the new millennium. The NICHD defines health disparities as differences in health and developmental outcomes, particularly between and among racial and ethnic groups. The facts: despite a 40-percent overall decline in SIDS deaths, the rate among American Indians (1.5/1,000) and African Americans (1.4/1,000) remains more than twice that of Whites (0.6/1,000). In addition, many of the risk factors for SIDS are more prevalent among American Indians and African Americans than Whites. In contrast, infants born to Hispanic and Asian or Pacific Islander mothers have among the lowest SIDS rates (0.4/1,000) of any racial or ethnic group in the United States. Moreover, overall rates vary within racial and ethnic groups. The Indian Health Service reports, for example, that the SIDS rate is 3.5/1,000 in the Aberdeen area of North and South Dakota, Iowa, and Nebraska, 1.6/1,000 in the Phoenix area, and 0.78/1,000 among the Navajo.

Research and intervention into this complex problem require new ways of thinking and multidisciplinary approaches. The overall goal guiding research into health disparities is to understand the mechanisms through which racial and ethnic differences occur due to complex interactions between basic biological processes and factors such as poverty, education, and “community” with its distinct geographic, environmental,

and cultural realities. Disparities between American Indians and Whites and between African Americans and Whites in regard to SIDS have, in part, been attributed to the higher level of poverty in these minority populations. The poverty rate, for example, among African Americans is more than twice that among Whites. For American Indians residing on a reservation, the poverty rate is 2.4 times that of the general U.S. figure of 13.1 percent. Aberdeen, Navajo, Billings, Albuquerque, and Phoenix all have poverty rates exceeding 40.0 percent. More specifically, 13.4 percent of American Indian women age 16 and older are unemployed, in contrast with 6.2 percent of women of all races nationwide.



Epidemiologic studies of SIDS prevalence rates have demonstrated the relevance of the following risk factors for SIDS: low family income; low parental educational levels; young (teenage) maternal age; maternal single marital status; few and often late prenatal healthcare visits; maternal illicit drug, alcohol, and/or cigarette intake during pregnancy; the presence of sexually transmitted diseases in mothers; and the absence of a telephone in the home. These risk factors are more common in impoverished communities than in the general population as a whole. Another major risk factor for SIDS is low birth weight. Disparities among different racial and ethnic groups likewise occur here: African American infants are more than twice as likely to be born with a low birthweight (<2500g) and more than 3 times as likely to be born with a very low birthweight (<1500g) than are white neonates. Of note, the higher incidence of low birthweight rate among African American infants cannot be explained by socioeconomic factors alone.

The remoteness of many American Indian reservations and other types of rural communities frequently affects access to preconceptional, prenatal, and postnatal health care. It likewise affects the coroner's system and the correct diagnosis of SIDS, since it magnifies the difficulties in performing a proper death scene investigation. In addition, the inequity of care evident in the coroner's system on the reservation is exacerbated by improper, and in some instances a complete lack of, training of the coroner and other personnel responsible for examining sudden infant deaths. Inconsistencies in death scene investigations also often result from the frequent turnover of coroners in rural areas.

Lack of access to care, inequities in the quality of care, and other barriers are more common in minority communities. It is not known to what extent these factors contribute to disparities in SIDS risk and prevalence rates. Such factors need to be examined through further

research. Moreover, it is unclear whether perceptions of racial discrimination or reported incidences of discrimination affect the maternal-fetal environment. Given the complexity of our social systems and the potential negative effects these factors may have on the lives of infants and their families, it is imperative that we continue to support efforts exploring these issues.

Little is also known about the protective factors that operate within certain poor minority communities to decrease SIDS risk. Why do Hispanics and some American Indian populations have low SIDS rates, despite adverse socioeconomic circumstances?

Differences in SIDS rates among racial and ethnic groups cannot be explained by social or economic inequalities alone. For example, when epidemiologists correct for socioeconomic factors, an excess risk for SIDS remains in the African American and American Indian populations. This observation suggests that biological factors—e.g., susceptibility genes—may play important roles in the pathogenesis of SIDS in specific racial and ethnic groups; certain genes predisposing infants to premature birth or sudden death may prove to be more prevalent in some populations than in others.

Such susceptibility genes may interact with environmental factors to trigger a cascade of intrinsic biological events that lead to sudden death. It has been reported, for example, that nicotine from tobacco smoke is metabolized more slowly in African American populations. This putative genetic variation suggests that toxic levels of nicotine may accumulate more rapidly in African American fetuses exposed to maternal cigarette smoking during pregnancy, thereby having a more deleterious effect on their growth and development. Thus, maternal cigarette smoking during pregnancy may make a greater contribution to the risk of SIDS among African Americans than it does among whites. It is also well recognized that SIDS is a syndrome and that there may be more than one mechanism of sudden death.

Thus, there may be factors unique to the pathogenesis of SIDS in individual racial or ethnic groups that must be considered in order to elucidate pathogenic mechanisms and the development of preventive strategies.

Differences in SIDS rates between racial and ethnic groups need not relate to socioeconomic and/or genetic factors alone. They may involve community traditions and cultural practices as well, particularly those involving methods of child care. For the message of the *Back to Sleep* campaign to be heard and acted upon, those delivering the message must be community-based and culturally sensitive.

Given the complexity of the problem of health disparities in regard to SIDS, multidisciplinary approaches to research into relevant social, economic, environmental, genetic, and cultural factors are essential. Multidisciplinary teams are needed to investigate both the protective and adverse factors operating within and across populations. For ultimate success, the multidisciplinary research approach must be linked to community involvement at all levels.

Research

Background

- Despite 40-percent declines in SIDS rates across all populations over the period of the *Back to Sleep* campaign, the rate of SIDS among African Americans and American Indians is still at least twice that of whites.
- Some risk factors for SIDS are more common among the economically disadvantaged, who are disproportionately represented among racial and ethnic minorities. These factors include maternal and paternal education of less than 12 years, late or no

prenatal care, maternal age below 20 at the time of the first pregnancy, and maternal single marital status.

- The rates of low birthweight and preterm birth are twice as high among African Americans as among Whites. These factors increase the risk for SIDS threefold.
- Bed sharing is more common among minority populations. Bed sharing has been shown to increase the risk for SIDS under the following conditions: when the mother smokes, when she has recently consumed alcohol, when the infant is covered by a quilt, and when parents are fatigued.
- Preliminary results from a study of SIDS among Northern Plains Indians demonstrate strong associations between prenatal binge drinking and SIDS and between the use of multiple layers of clothing and SIDS.
- Even after adjusting for socioeconomic factors and cigarette smoking, African Americans, American Indians, and Alaskan Natives are at increased risk for SIDS.

Goals and Objectives

Goal: Identify the mechanisms underlying racial and ethnic disparities in SIDS rates.

- **Objective:** Support research that focuses on environmental, biological, and cultural factors related to SIDS within specific minority populations and develop partnerships with these populations. The analysis of data can be approached in at least two different ways: (1) within the context of the minority population itself and (2) in comparison with other racial and ethnic populations. Design studies to address the potential role of race and/or ethnicity as an independent risk factor for SIDS, as a modifier of

other known risk factors, and as a confounder or intervening event in the natural history of SIDS.

- **Objective:** Support research that delineates the contribution of genetic and environmental factors that influence the risk of SIDS, including potential gene-environment interactions.
- **Objective:** Investigate the role of inequities in prenatal and postnatal health care that are contributing to the disparate SIDS rates evident in various racial and ethnic groups.
- **Objective:** Investigate the role of culturally specific patterns of infant care practices in disparate SIDS rates among racial and ethnic groups. Such care practices include infant sleep position, bed sharing, and types of bedding.

Interventions

Background

- Between 1992 and 1998, the proportion of infants placed to sleep on their stomachs declined from 70 percent to 17 percent. Among African Americans in the survey population, however, the decline was significantly less: from 82 percent to 32 percent.
- After adjusting for socioeconomic factors, and for whether they received a recommendation to place infants on their backs to sleep, African Americans were twice as likely to place infants on their stomachs and half as likely to place infants on their backs as compared with Whites.
- Between 1992 and 1998, the SIDS rate among African Americans decreased by almost 40 percent, a magnitude similar to that observed in the White

population. Nonetheless, the SIDS rate among African Americans remained twice that of whites.

- Within the Hispanic and American Indian populations, there are subpopulations based on country of origin or tribe that are more likely to place babies on their stomachs to sleep rather than on their backs.
- Sleeping on soft bedding is a significant SIDS risk factor among all minority populations. The use of soft bedding has not changed appreciably since the initiation of the *Back to Sleep* campaign and the release of recommendations from the AAP and CPSC to remove soft bedding from the crib.
- In 1999, the *Back to Sleep* campaign initiated an outreach component aimed at the African American community. It formed a partnership with the National Black Child Development Institute and other African American leadership organizations to develop a community-linked campaign.
- In 2000, a "Resource Kit for Reducing the Risk of SIDS in African American Communities" was produced and a plan for national and local training programs was developed. In 2001, training activities through the affiliate organizations began.

Goals and Objectives

Goal: Improve the dissemination and adoption of the *Back to Sleep* campaign recommendations among minority populations in the United States.

- **Objective:** Integrate knowledge of cultural practices and beliefs into approaches formulated to reach specific minority populations.

- **Objective:** Continue to develop strategies for community input into the development and implementation of campaign activities.
 - Conduct training workshops and educational sessions with health professionals, community leaders, outreach workers, and individuals to develop methods for working locally in SIDS risk-reduction activities.
 - Work on existing health promotion projects within organizations that will enhance their scope and infrastructure by incorporating SIDS risk reduction strategies.
 - Among American Indian communities, involve tribal programs and services provided by the Indian Health Service. Tribal educators are often the keys to communication with local communities. Universities, colleges and tribal community colleges can also offer important resources.
- **Objective:** Evaluate the process of information dissemination, behavioral change, and health outcomes at the national and local levels among minority populations.
 - Provide this information to community organizations to stimulate the adoption and revision of SIDS risk-reduction strategies.

Goal: Reduce disparities in SIDS rates that may be related to risks not targeted by the *Back to Sleep* campaign.

- **Objective:** Develop a dialogue with partnership organizations to identify potential sources of risk within specific communities. Disseminate research data relevant to specific communities in order to support existing health promotion programs or to develop interventions. An example is the reduction of prenatal alcohol exposure among some American Indian tribal communities.

Infrastructure

Background

- The infrastructure necessary to perform research in health disparities in SIDS rates is complex and involves novel multidisciplinary approaches.
- Innovative programs currently exist that provide models for community partnerships aimed at reducing disparities in SIDS rates: e.g., the interrelationship among the Women's Health Program of the Aberdeen Area, Healthy Start, Indian Health Service hospitals and clinics, and the Maternal and Child Health Division of the state of South Dakota.
- The NICHD has already established two national "Brain and Tissue Banks for Developmental Disorders" that include specimens taken from infants who died of SIDS. These banks should be expanded to permit genetic analyses of tissues within and between different racial and ethnic groups.
- Innovative methods exist for developing mentoring programs to encourage minority middle school, high school, college, and graduate students to enter the health professions, and conduct health-related research focused on their communities: e.g., the Four Directions Program for American Indian college students at Harvard Medical School.

Goals and Objectives

Goal: Develop and sustain community partnerships for research and intervention in an effort to reduce disparate SIDS rates in minority populations.

- **Objective:** Support partnerships between academic institutions and community organizations for research, the training of minority investigators, and the dissemination of research findings in minority communities.

- **Objective:** Develop partnerships with organizations and other significant community leaders at the national, regional, state, and community levels to collaborate in the design of materials and initiatives in their geographic areas.
- **Objective:** Provide leadership to partner organizations in coordinating regional summits and in enlisting the resources of community organizations, faith-based groups, public health officials, and service organizations to reduce the risk of SIDS.



Goal: Facilitate the definition of risk profiles for SIDS in different racial and ethnic groups by conducting large-scale epidemiologic studies within and across populations.

- **Objective:** Develop web-based data management strategies for conducting research. This technology permits simultaneously-conducted studies and employs standardized methods, while allowing investigators continual access to all aspects of an ongoing study.
- **Objective:** Investigate promising new medical informatics technologies to identify critical data or research gaps.
- **Objective:** Foster the use of new research designs and analytic tools well suited to the identification of triggers for SIDS or the possible repetition of adverse pregnancy outcomes in families. Case crossover designs, for example, might prove useful in identifying factors that increase SIDS risk.

Goal: Recruit minority researchers in basic health sciences and applied clinical care, as well as in the social and behavioral disciplines, to conduct SIDS research.

- **Objective:** Develop mentoring programs at the middle school and high school levels for minority students in the relevant health and social science disciplines.
- **Objective:** Develop targeted mentoring programs in SIDS research at the graduate and postdoctoral level for minority students already trained in the relevant health and social science disciplines.

Appendix—Roster of Advisors

Although this document has benefited from the input of many scientists within and outside the NICHD, and from the general public, we wish to particularly note the advice of the following members of the SIDS strategic plan working group:

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Forget Me Not

The little one no longer here
comes quietly in the morning sun
reminding me of midday walks
and midnight feedings.

The little one no longer here
sits quietly in my heart
whispering in my dreams
forget me not.

Debbie Gemmill
from *The Chance to
Say Goodbye*
Beachcomber Press, 1991

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