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SUDDEN INFANT DEATH SYNDROME

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"And this woman's son died in the night ..."

1 Kings 3:19

INTRODUCTION

For nearly 3,000 years, it has been recognized that apparently healthy infants could die suddenly and unexpectedly during their sleep. Throughout most of history, it was believed that these infants somehow suffocated, either by maternal overlaying or by strangling in bedclothes. Although these explanations have largely been discarded, nearly one infant per thousand live births continues to die suddenly and unexpectedly.

Sudden infant death syndrome (SIDS) is the sudden death of an infant under one-year of age, which remains unexplained after performance of a complete postmortem investigation, including an autopsy, examination of the death scene, and review of the case history¹. SIDS is the most common cause of death in infants between the ages of one-month and one-year, affecting nearly one out of every 1,000 live births^{2,3,4}. This accounts for nearly 3,000 SIDS deaths in the United States per year, or approximately one baby every 3-hours of the day and night! Unfortunately, SIDS is not a rare occurrence in the general population. The peak incidence is between 2 and 4 months of age. Approximately 95% of SIDS deaths occur before the age of 6-months, but SIDS deaths can occur until one-year of age^{2,3,4}.

A typical clinical course for a SIDS death is that the parents or caregivers put their infant to sleep, either at night or during a daytime nap^{2,3,4}. They return at some later time to find that the infant has died unexpectedly. Usually, these infants were healthy prior to death, although some had evidence of a mild upper respiratory infection. SIDS deaths have occurred when parents or caregivers have placed their infants down for a nap, have been within hearing distance of the infant the entire time, and have returned as briefly as 20-minutes later to find that their infant has died. Yet, these parents report hearing no signs of a struggle. Thus, SIDS deaths appear to occur swiftly and silently.

Table 1: CALIFORNIA AND U.S. SIDS RATES 1980-98

Year	CALIFORNIA			U.S.A.
	Live Births	SIDS Deaths	SIDS Rate*	SIDS Rate*
1980	402,720	668	1.66	1.53
1981	420,418	610	1.45	1.46
1982	429,631	636	1.48	1.44
1983	435,722	650	1.49	1.46
1984	447,394	630	1.41	1.43
1985	470,816	682	1.45	1.41
1986	481,905	651	1.35	1.41
1987	503,376	661	1.31	1.37
1988	532,708	725	1.36	1.40
1989	569,308	780	1.37	1.39
1990	611,666	716	1.17	1.30
1991	609,228	724	1.19	1.30
1992	600,838	568	0.95	1.20
1993	584,483	545	0.93	1.17
1994	567,034	486	0.86	1.03
1995	551,226	397	0.72	0.84
1996	538,628	311	0.58	0.78
1997	534,174	328	0.63	0.69
1998	521,265	259	0.50	0.64
1999	518,073	237	0.46	0.67
2000	531,285	222	0.42	0.53

* SIDS Rate is SIDS deaths per 1000 live births.

Carrie Florez, Anna Figueroa, and Donna Steen, California SIDS Program,
California Department of Health Services, 2002.

By definition, the etiology of SIDS is not known^{1,2,3,4}. In approximately 15%-20% of infants who die suddenly and unexpectedly, a conventionally accepted cause for the death is found at postmortem examination. These infants are not said to have died from SIDS, but rather from the cause of death found. This leaves 80%-85% of infants who died suddenly and unexpectedly in whom no cause of death can be found at postmortem examination. These infants comprise the group called *SIDS*.

ONE CAUSE OR MANY?

SIDS has often been referred to as a *diagnosis of exclusion*. That is, the pathologist looks for identifiable causes of death. If none are found, then, by exclusion, the diagnosis of *SIDS* is made. Is SIDS due to one cause or many? Some unique and characteristic epidemiologic features about most SIDS deaths suggest that most babies dying from SIDS die from the same final common mechanism or final common pathway of death ².

SIDS has a unique age distribution. The peak incidence of SIDS is between 2 and 4 months of age. Infants are relatively spared in the first 1-2 months of life, and 95% of SIDS deaths occur before 6 months of age. For other natural causes of infant death, the rate is highest near birth, and decreases thereafter ^{2,3,4}. SIDS also has a unique seasonal distribution, which is not shared by other natural causes of infant death ^{2,3,4}. SIDS is more common in winter months and less common in the summer. If SIDS was simply a collection of other natural causes of infant death, one would not expect these unique age and seasonal distributions. Thus, epidemiologic evidence favors the hypothesis that the majority of SIDS victims died from a single common mechanism of death, although many "triggers" might lead an infant into that final common pathway.

EPIDEMIOLOGIC STUDIES

Epidemiologic studies have been performed in an attempt to identify *risk factors* for SIDS ^{2,3,4,5}. When risk factors are found in a population, the statistical risk of SIDS occurring in that population increases. However, *risk factors* are not *causes* of SIDS. They may provide *clues* for researchers to the cause of SIDS. Therefore, they are important for research ⁵. However, no risk factor, singly or in combination, is sufficiently precise to predict the baby who will die from SIDS. Further, most SIDS victims had few, if any, *risk factors* prior to death.

Maternal factors associated with a statistically increased risk for SIDS include: cigarette smoking or substance abuse (specifically opiates or cocaine) during pregnancy ⁶, teen-aged and older mothers, birth order, short inter-pregnancy intervals, delay in initiating prenatal care, unmarried mothers, low blood pressure during the third trimester of pregnancy, and high or low hemoglobin during late gestation ^{4,7}. SIDS is more common in lower socioeconomic groups and certain racial groups ^{3,4}. Although these studies do not point to a specific etiology, they suggest that infants who had a suboptimal intrauterine environment may be at a higher risk of dying from SIDS ³.

Infant factors, which are associated with a statistically increased risk for SIDS, include: preterm infants ⁸, low birthweight infants ⁸, multiple gestation (twins, triplets, etc.) ^{9,10,11}, and prone sleeping. Often, SIDS deaths are temporally associated with viral respiratory infections ^{2,3,4}.

POST-MORTEM EXAMINATION IN SIDS

By definition, an identifiable cause of death is not found at post-mortem examination ^{1,2,3,4}. The autopsy of a SIDS victim shows the absence of other serious illness which could contribute to the death, no signs of severe illness, and no signs of significant stress. However, common post-mortem findings in the SIDS victim include: intrathoracic petechiae; pulmonary congestion and edema; minor airway inflammation; minimal stress effects in the thymus and adrenal glands; normal nutrition and development; fluid blood; and an empty urinary bladder ^{2,4}. The significance of the latter four of these findings is that these infants were generally healthy prior to death. The autopsy should be performed by a qualified pathologist, preferably using a uniform autopsy protocol ¹². Neither epidemiologic studies nor the post-mortem findings have resulted in a generally accepted

cause for SIDS. The cause remains unknown^{1,2,3,4}, though current research efforts are making advances in our knowledge which may ultimately lead to this answer.

RESEARCH INTO POSSIBLE CAUSES OF SIDS

The cause of SIDS is unknown. Much of SIDS research has searched for a single abnormality or disorder in a single physiological system. Is SIDS caused by one abnormality in one physiologic system? Do some infants have a pre-existing abnormality which predisposes them to die from SIDS? Will those infants who do not have this pre-existing abnormality not die from SIDS? This point is controversial. Some believe that SIDS victims were not normal, but that they had a pre-existing abnormality which predisposed them to die. Other researchers believe that SIDS can happen to any infant, and is the result of interactions between development, infant physiology, and environmental factors. This section will review research which investigates cardiac, metabolic, respiratory, arousal, and hypoxic causes of, or contributors to, SIDS.

EVIDENCE FOR CARDIAC CAUSES OF SIDS

When one thinks of sudden death, the heart is often the first focus of attention. Cardiac arrhythmias can cause sudden death, but are not likely to be detected at post-mortem examination^{3,12,13}. The Long Q-T Interval Syndrome can cause intermittent lethal ventricular fibrillation^{13,14}. The clinical syndrome of prolonged QT interval appears to have a genetic basis, and is much more rare than SIDS¹⁵. However, Schwartz and coworkers recorded ECGs in 34,442 infants within the first week of life¹⁴. Twenty-four subsequently died from SIDS, and 12 (50%) had a prolongation of the corrected QT interval. This important study suggests a possible cardiac mechanism for SIDS¹⁴. However, it is unclear how to handle an infant with an identified prolonged QT interval, even if one advocated prospective ECG screening of all infants^{14,15}. Further, the prolonged QT interval hypothesis does not explain the unique age distribution for SIDS, it does not explain why SIDS deaths occur during sleep (since most prolonged QT interval syndrome deaths occur with exercise), and it does not explain the success of back sleeping at reducing the SIDS rate. Therefore, the prolonged QT interval syndrome does not explain all the facts about SIDS. However, this compelling study deserves more research effort. Newborn screening for the prolonged QT interval is not likely to significantly reduce SIDS deaths, and is not currently recommended¹⁵.

Some infants, judged to be at high risk for SIDS, for whom home apnea-bradycardia monitors were prescribed, subsequently died while using these monitors. These physiologic recordings at the time of death appear to demonstrate an abrupt bradycardia¹⁶. However, there is some debate over the interpretation of these tracings. Kelly and coworkers also found that tachycardia often preceded the terminal SIDS episode¹⁷. In some cases, this occurred within minutes of the event 83% of terminal events began with a severe, abrupt decrease in heart rate followed by irregular breathing¹⁸. 11% of events began with apnea followed by bradycardia 5% of events began with simultaneous bradycardia and apnea¹⁸. Infants could not be resuscitated from this bradycardia. This may indicate some autonomic nervous system abnormality in these babies who died from SIDS. However, all babies in this study were placed on home monitoring for clinical indications, thus they may not represent the *typical* SIDS victim who does not begin with high risk factors.

Studies have shown decreased beat-to-beat heart rate variability in infants at high risk for SIDS, and in infants who have died from SIDS^{19,20,21}. These results are interpreted as an abnormal autonomic nervous system function controlling heart rate variability, rather than a primary

cardiac abnormality^{19,20,21}. They suggest that these SIDS infants have a decreased ability to change heart rate in response to environmental challenges.

In summary, an isolated abnormality in the cardiac system has not been identified which adequately explains the cause of SIDS.

METABOLIC DISORDERS AS CAUSES OF SIDS

Some have suggested that inborn errors of metabolism may be an important cause of SIDS. Medium chain Acyl-CoA dehydrogenase deficiency (MCADD) is a relatively common inherited metabolic disorder of beta-oxidation of fatty acids, although over 10-times less common than SIDS. The presence of this disorder prevents the conversion of ingested fats into energy. While infants can often do quite well with the absence of this enzyme, it is necessary during times of fasting or stress. MCADD has been suggested to be an important cause of SIDS. However, Arens and coworkers performed DNA diagnostic testing in an attempt to detect MCADD in all SIDS victims in Los Angeles County over 6-years (approximately 1200). No MCADD were found in any SIDS victim²². Thus, MCADD does not appear to be a frequent cause of SIDS. However, other metabolic disorders may still cause SIDS. Boles and coworkers used biochemical techniques to analyze liver tissue from 313 SIDS victims from the State of Maryland²³. They found that 14 SIDS victims had findings suggesting some metabolic disorder in fatty acid oxidation (of which MCADD is the most common). They concluded that metabolic errors may explain approximately 5% of SIDS deaths²³. However, the diagnostic criteria for SIDS were not specified in Boles' article. Fatty liver infiltration, for example, may cause some coroners to diagnose an inborn error of metabolism, and others to diagnose SIDS. Boles' study does emphasize that inborn errors of metabolism can cause sudden death in infants. It is reasonable to screen for this, once a practical and inexpensive screening technique is available for large numbers of infants²⁴. However, it appears that metabolic disorders are not as common in SIDS babies, where fatty liver infiltration would lead the coroner to make a non-SIDS diagnosis. In addition to causing sudden death, inborn errors of beta-oxidation of fatty acids were found in approximately 4% of infants with severe apparent life-threatening events²⁵.

In summary, inborn errors of metabolism have not been identified which adequately explain the cause of the majority of SIDS deaths.

EVIDENCE FOR RESPIRATORY CAUSES OF SIDS

The infant respiratory system is developmentally immature and rapidly changing. From an engineering perspective, a rapidly changing system is intrinsically unstable²⁶. Even in healthy infants, neurologic control of breathing is unstable. Ventilation is depressed by hypoxia, and immature reflexes cause apnea. Immaturity of the lungs predisposes to atelectasis, airway obstruction, pulmonary hypertension, and edema. The upper airway is predisposed to collapse, causing obstructive apnea during sleep. Chest wall instability causes decreased lung volume and increased work of breathing. Ventilatory muscle strength and endurance are decreased, resulting in ventilatory muscle fatigue. Thus, normal infants, *without* increased risk for SIDS, can have apneas at least 20-seconds in duration during sleep.

There is a great deal of circumstantial evidence suggesting that respiratory mechanisms are important in SIDS. Cessation of breathing (apnea) can cause sudden death, which may not be detected at post-mortem examination¹¹. Thus, it fits the definition of SIDS. Respiratory disorders can be categorized in terms of how they affect the respiratory system.

PRIMARY LUNG DISEASE

A lung disease sufficient to cause death would likely be detectable at autopsy. Thus, SIDS is not likely due to a single lung disease. However, common post-mortem findings in the SIDS victim include intrathoracic petechiae, pulmonary congestion and edema, and minor airway inflammation¹¹. While not generally considered to be severe enough to have caused death, these findings raise the possibility that lung disease has a role in SIDS. Martinez hypothesized that the small airways of infants are predisposed to collapse, and that increased resistance of small airways could cause sudden death by progressive peripheral bronchial occlusion²⁷. The presumed trigger for this chain of events is an acute viral lower respiratory tract illness causing inflammation²⁷. Susceptible infants are believed to have decreased airway conductance (increased resistance) due to congenital and environmental factors²⁷. Kao measured lung function in ten infants with unexplained apnea, a group of infants with a statistically increased risk for SIDS²⁸. She found that specific airway conductance was decreased, suggesting airway obstruction, lending support to the Martinez hypothesis.

Morley and others have described surfactant abnormalities in SIDS victims, which would predispose to atelectasis^{29,30,31}. If other mechanisms which maintain the functional residual capacity in babies are compromised, then larger areas of lung collapse may occur, causing hypoxia. These results would predict that lung compliance is low in SIDS victims, but Fagan and Milner found normal pressure-volume loops in SIDS victims post-mortem³². Thus, Morley speculated that this surfactant abnormality causes physiologic lung dysfunction during life, but that the physiologic consequences of these surfactant abnormalities are difficult to measure post-mortem^{29,30,33}. The cause of these surfactant abnormalities in SIDS is not known. Morley speculates that it could be related to viral infections of the lung³⁴. Even if surfactant abnormalities are not the sole cause for SIDS, they may be a contributor to the mechanism of death in SIDS and/or provide a mechanism how viral infections may be associated with SIDS.

In general, SIDS victims do not manifest symptoms of chronic lung disease prior to death. However, infants with chronic lung disease, bronchopulmonary dysplasia, do have an increased risk for SIDS^{35,36,37}, suggesting that abnormal lung function may contribute to the mechanism causing SIDS.

VENTILATORY MUSCLE WEAKNESS OR FATIGUE

There has been little research on ventilatory muscles in SIDS. Keens described a "normal" maturational pattern of increasing fatigue-resistant muscle fiber types in the human diaphragm and intercostal muscles over the first year of life³⁸. However, he used autopsy samples, and nearly all infant diaphragms were derived from SIDS victims. Thus, it is not clear whether this increase in the first year of life is normal, or is aberrant and a characteristic of SIDS³⁸. Scott measured maximal transdiaphragmatic pressure, as a measure of diaphragm strength, in infants with unexplained apnea³⁹. He found that diaphragm strength was not decreased, but rather it was significantly increased compared to controls. This could be interpreted as representing ventilatory muscle training in response to lung disease or upper airway obstruction. However, there is no evidence supporting a primary ventilatory muscle dysfunction as the cause of SIDS.

UPPER AIRWAY OBSTRUCTION

A common autopsy finding in SIDS victims is the presence of intrathoracic petechiae on the thymus, lungs, pleural surfaces, and heart^{40,41}. Extrathoracic portions of the thymus do not show

petechiae. These intrathoracic petechiae may have been formed by the generation of highly negative intrathoracic pressures, as might occur when an infant attempts to breathe against upper airway obstruction⁴¹. Intrathoracic petechiae suggest that obstructive apnea may be involved in the final mechanism of SIDS deaths⁴¹.

The anatomy of the infant's upper airway and relatively increased amount of active sleep predisposes infants to upper airway obstruction^{42,43,44,45}. Traditionally, SIDS researchers have been concerned about central apnea possibly causing death in infants^{46,47,48}. However, obstructive apneas have more recently been identified in infants at increased risk for SIDS^{49,50}. Kahn and coworkers examined overnight polysomnographic recordings from 30 infants who subsequently died from SIDS, and compared them with recordings from 60 matched control infants⁴⁹. They found significantly more and longer obstructive breathing events in the SIDS infants⁴⁹. Obstructive events were accompanied by bradycardia and hypoxemia. Central apneas were not different between the two groups. Tishler and associates have identified an increased family history of sudden unexpected infant deaths in adults with the obstructive sleep apnea syndrome, and have hypothesized a familial association between the two⁵¹. In the past, recordings performed in the home on infants who subsequently died from SIDS, or who are at risk from SIDS, have not had the technical capability to detect obstructive apneas. Therefore, the question of the importance of obstructive apnea in SIDS remains unanswered.

VENTILATORY CONTROL DISORDERS

Infants with unexplained apnea have an increased risk of dying from SIDS^{46,47,48,52,53}. Tissue markers of chronic hypoxia and hypoxemia have been described in many SIDS victims by some investigators^{54,55,56,57,58,59,60}. Brainstem lesions have been seen in areas controlling ventilation and sleep/wakefulness in many SIDS victims^{61,62,63}. Many infants at high risk for SIDS have ventilatory control disorders^{46,47,64,65}. While these findings do not prove that SIDS is due to a respiratory disorder, there is considerable circumstantial evidence suggesting that SIDS may involve abnormal neurologic control of breathing^{44,45}.

The circumstantial evidence in favor of respiratory causes for SIDS prompted many investigators to formulate the apnea hypothesis of SIDS. The simplistic version of this hypothesis says: 1) SIDS occurs when infants stop breathing during sleep^{46,47,48,52,53,64}. 2) One can test infants to see if they have apneas 3) Infants with increased apnea during sleep are at high risk for SIDS and should be treated or protected^{46,47}. Home apnea-bradycardia monitoring, which sounds an alarm to summon trained parents when an infant has a prolonged apnea or bradycardia, has been advocated as the preferred method to protect these infants⁴⁷. However, relatively few SIDS victims had any previous apneas observed prior to death⁶⁶. Prospective studies of the sleeping ventilatory pattern do not predict SIDS or death in infants^{37,53,67}. Home apnea-bradycardia monitoring and infant apnea evaluations have not substantially decreased the SIDS rates for the general population⁶⁶. Thus, the simplistic approach to treating apnea in infants has not decreased SIDS. However, it is still possible that SIDS involves a respiratory disorder.

Kinney and others have found gliosis and subtle changes in brainstem centers responsible for control of breathing and control of sleep/wakefulness^{57,61,62,63}. More recently, she has found a decrease in muscarinic cholinergic receptors and kainate receptors in the arcuate nucleus of the brainstem in SIDS victims^{62,63}. This area of the brainstem is thought to be related to the physiologic responsiveness to increased CO₂. These findings suggest that the origins of SIDS may lie in abnormal control of breathing or abnormalities in regulation of sleep/wakefulness^{44,45,62,63}.

However, these theories remain unproven.

The study of genes which may affect control of breathing could improve our understanding of SIDS. Brain-derived neurotrophic factor (BDNF) may be important in determining the development of control of breathing⁶⁸. Infant mice which lack the gene for BDNF have a loss of neurons responsible for normal ventilatory control. These mice appear to demonstrate an abnormality in carotid body, or peripheral chemoreceptor, function, which provides a chronic stimulus to breathing, and is the body's primary sensor of low oxygen. Infant mice without the BDNF gene breathe slower and shallower, and do not respond to hypoxia⁶⁸. BDNF deficient mice showed a normal response to elevated CO₂, suggesting that the BDNF gene is not active in the CO₂ response. Thus, the BDNF gene may control the development and/or survival of nerve cells in the carotid body, which affect a baby's protective response to low oxygen⁶⁸. It is unclear how this may relate to SIDS, and studies have not been performed in SIDS victims. In the near future, it is likely that other genes will be described which affect control of breathing. While it is tempting to postulate a genetic etiology to SIDS⁵¹, studies in twins^{9,11} and in SIDS siblings^{53,69,70,71,72} do not convincingly suggest that SIDS is hereditary.

AROUSAL RESPONSES TO RESPIRATORY STIMULI

Arousal from sleep is an important defense mechanism against danger-signaling stimuli during sleep. All infants have frequent breathing pauses during sleep. The inability to arouse from sleep in response to an apnea or hypoxia could prevent an infant from terminating an apnea, resulting in death^{65,73,74,75}. The process of changing from sleep to wakefulness (arousal) is associated with many changes in the respiratory system which improve breathing⁴⁵. Thus, arousal is a logical defense mechanism to protect breathing during sleep.

Preliminary evidence suggested that infants at high risk for SIDS had abnormal arousal responses to hypoxia^{65,74,76,77,78}. These same infants also had alterations in circulating catecholamine levels^{74,79}. However, normal control infants also often fail to arouse in response to hypoxia^{75,80}. Normal infants arouse frequently under 9-weeks of age, but not between 9-weeks and 6-months of age⁷⁵. This corresponds to the peak age distribution for SIDS. It is possible that infants are born with a protective brainstem-mediated hypoxic arousal response, which is inhibited by increasing cortical development after 2-months of age. However, this is quite preliminary, and not proven. Other factors also affect arousal. For example, repetitive hypoxic events depress the arousal response to hypoxia^{74,81}. Thus, infants with frequent hypoxic events may depress their protective arousal responses and increase their risk of death^{65,75}. A great deal more work is required to establish a link between these altered arousal patterns and SIDS^{65,73,74,75,76,77}.

McNamara and coworkers tested the arousal response of 10 healthy infants to tactile stimuli⁸². Arousal could be abolished by repeated exposure (habituation)⁸². While brainstem and spinal mediated responses were more resistant to habituation than cortically mediated responses, even they were eventually inhibited. As mentioned, repeated exposure to hypoxia blunted hypoxic arousal responses^{74,81}. Thus, habituation of the infant arousal response to repeated stimuli, especially hypoxia, hypercapnia, or airway occlusion, may be relevant to SIDS^{74,81,82}.

Prenatal and postnatal exposure to cigarette smoking are now recognized as significant risk factors for SIDS⁸³. Infants born to cigarette smoking mothers have higher arousal thresholds to auditory stimuli than infants not so exposed⁸⁴. Thus, decreased arousal is associated with an important risk factor for SIDS.

ROLE OF HYPOXIA IN SIDS

Tissue markers of chronic hypoxia and hypoxemia have been described in many SIDS victims by some investigators^{54,55,56,57,58,59,60}. While some of these findings are controversial, the search for evidence of chronic hypoxia as a cause of SIDS is an active area of research.

The transition from fetal life to post-natal life is associated with changes in the oxygen, CO₂, and acid environment. The most marked change at birth is an increase in oxygen from a Po₂ of 20-25 torr *in utero* to much higher levels of 60-90 torr after birth. At the moment of birth, blood gas values suggest that there should be powerful chemoreceptor drive from hypoxia¹⁴⁸. However, peripheral chemoreceptors do not seem to be required for the initiation of air breathing¹⁴⁹, and they are probably quickly inhibited by the rapid increase in Po₂ at birth. Thus, neonates have decreased ventilatory responses to hypoxia in the first few days after birth¹⁴⁸. Resetting of the peripheral chemoreceptors occurs in response to the increased post-natal oxygen tension, and can be inhibited by maintaining persistent hypoxia¹⁵⁰.

Chemical and neurological control of breathing in infants are related to sleep state¹⁵¹. During quiet (NREM) sleep, breathing is regulated primarily by automatic ventilatory control, located in the brainstem. Thus, breathing is regular with respect to timing and amplitude¹⁵². Breathing is responsive and tightly linked to chemoreceptor input^{44,45}. However, during active (REM) sleep, breathing is controlled primarily by the voluntary or behavioral system, and it is not tightly regulated by chemoreceptor input. Thus, breathing is irregular with respect to timing and amplitude. Periodic breathing occurs frequently in wakefulness, quiet sleep, and active sleep, but its prevalence is greater in active (REM) sleep¹⁵³. Periodic breathing tends to be more regular in quiet (NREM) sleep than in active (REM) sleep^{154,155}. However, minute ventilation is increased in REM sleep due to an increase in respiratory rate, with little change in tidal volume, compared to NREM sleep^{153,154,155}.

A decrease in inspired oxygen increases ventilation initially in neonates, followed by a later decrease^{156,157,158,159}. In adults, the increase in ventilation is more sustained¹⁶⁰. Newborn infants have less ventilatory response to hypoxia than older infants. In newborn infants, the hypoxic ventilatory response is similar initially in wakefulness, REM and NREM sleep, but it is sustained longer in NREM sleep¹⁵³. In preterm infants breathing F_{IO2} 0.15, there is a sustained increase in ventilation during quiet (NREM) sleep, a transient increase followed by a decrease in wakefulness, and predominantly a decrease in active (REM) sleep¹⁶¹. This probably reflects the tighter coupling between ventilation and chemoreceptor input during NREM sleep than during REM.

	Quiet (NREM) Sleep	Active (REM) Sleep
Neurologic Control	Automatic (Metabolic)	Behavioral (Voluntary)
Chemoreceptor Regulation	Tight	Poor
Timing of Ventilation	Regular	Irregular
Amplitude of Ventilation	Regular	Irregular
Periodic Breathing	Decreased; Regular	Increased; Irregular

The immediate increase in ventilation reflects an intact peripheral chemoreceptor response. The mechanism of the late decrease in ventilation with hypoxia is thought to be due to direct depression of the respiratory centers from hypoxia^{162,163}. Pco₂ also decreases in response to the

initial hyperventilation, which may contribute to the late depression in ventilation. However, when minute ventilation remains lower than baseline, Pco₂ remains low, suggesting that metabolic rate decreases in response to hypoxia¹⁶⁴. This reduction in CO₂ drive may be accentuated by the hypoxic cerebral vasodilatation, which would decrease brain tissue Pco₂ and depress ventilation. This mechanism would be expected to cause only a transient decrease in ventilation. However, the ventilatory depression to hypoxia in newborn kittens lasts 40-minutes¹⁶⁵. Further, the addition of CO₂ to inspired air does not abolish the biphasic hypoxic ventilatory response¹⁵⁸. Thus, the mechanism of the biphasic response is likely direct hypoxic depression of respiratory centers and a decrease in metabolic rate.

Changes in lung mechanics from hypoxia may also contribute to the ventilatory depression following hypoxia. Hypoxia decreases lung compliance, which would decrease ventilation^{158,166}. However, these changes in compliance are present during the initial phase of hypoxia when ventilation is stimulated, so lung mechanics do not completely explain the ventilatory depression¹⁶⁶. This biphasic ventilatory response of the infant to hypoxia suggests that if an infant becomes hypoxic, rather than stimulate breathing, hypoxia may serve to cause periodic breathing and/or apnea, by direct depression of central respiratory centers and reduction in metabolic rate^{157,164}. The addition of supplemental oxygen, even in low concentrations, will often decrease or eliminate these apneas.

At the peripheral chemoreceptors, hypoxia and hypercapnia act synergistically to stimulate ventilation. Centrally, hypoxia and hyperoxia have opposing effects Hypoxia increases cerebral blood flow, which decreases brain tissue Pco₂, and thus decreases ventilation Hyperoxia causes cerebral vasoconstriction, which increases tissue Pco₂, and thus increases ventilation.

	Hypoxia	Effect on Ventilation
Metabolic Rate	Decreases	Decreases
Brain Tissue	Depresses	Decreases
Peripheral Chemoreceptor	Stimulates	Increases
Cerebral Blood Flow	Increases	Decreases
Brain Tissue Pco ₂	Decreases	Decreases
Lung Compliance	Decreases	Decreases

The newborn ventilatory response to hypoxia is characterized by a late depression of ventilation, possibly due to direct hypoxic depression of central respiratory centers.

Neonates tolerate acute hypoxia or oxygen deprivation better than adults^{85,86}. Ninety-five percent of neonatal rats survived anoxia for 50-minutes, while all adults died within 4-minutes⁸⁷. This is not surprising since neonates have just come from an intrauterine environment where the mean oxygen tension is 26-30 torr. They have several adaptations to this hypoxic state, such as increased fetal hemoglobin. An important neonatal adaptation is that they have the ability to decrease oxygen consumption during hypoxia^{88,89}. Adults will increase ventilation in response to hypoxia (fight). However, neonates decrease their oxygen requirement in response to decreased oxygen substrate (accommodate), rather than try to increase available oxygen. Further, this decrease in oxygen consumption is not accompanied by an increase in anaerobic metabolism^{90,91}. Thus, oxygen consumption is decreased in response to the hypoxic state, and may not be simply a consequence of failure to supply enough oxygen for aerobic metabolism.

Although neonates tolerate hypoxia better than older children or adults, there is evidence that this tolerance is rapidly lost in infancy, when the incidence of SIDS increases. Infants have decreased tolerance for hypoxia compared to neonates. Infants have decreased ability to autoresuscitate (gasp) in response to anoxia than neonates or older animals⁹². Infants also have a shorter time to last gasp than neonates or adults⁹³. Infants have less ability to continue mitochondrial function during hypoxia than neonates or adults⁹⁴. Finally, peripheral chemoreceptor denervation is better tolerated by neonates and adults than by infants⁹⁵. Thus, the infant period, after the neonatal period, is associated with an increased vulnerability to hypoxia or anoxia and with an increased risk for SIDS.

Repeated exposure to hypoxia in infancy may be even more deleterious. Repeated exposure to hypoxia depresses the arousal response to hypoxia during sleep^{74,81}. Repeated exposure of newborn piglets to hypoxia also decreases their hypoxic ventilatory response compared to piglets exposed to continuous hypoxia⁹⁶. Repeated hypoxic exposure also decreases cardiac glycogen levels⁹⁷. Thus, repeated exposure to hypoxic events inhibits protective physiologic responses to hypoxia, making infants more vulnerable to the effects of a hypoxic event^{74,81,96,97}. Even normal infants have frequent hypoxic episodes during sleep, which may predispose them to the consequences of these repetitive hypoxic stresses⁹⁸. Infants with bronchopulmonary dysplasia are at increased risk for SIDS^{35,36,37}, and have frequent spontaneous hypoxic events⁹⁹. Although these infants have an intact hypoxic arousal response at term, they have an abnormal response to hypoxia after arousal leading to apnea and bradycardia¹⁰⁰. Thus, even when repeated hypoxia does not depress arousal responses, it may be associated with an inability to rescue oneself from hypoxia-induced apnea and bradycardia^{99,100}.

Compared to neonates, on the one hand, and older children and adults, on the other, infants have inadequate physiologic responses to protect against hypoxia, which may cause the infant to enter a physiologic pattern leading to death. Repeated exposure to short hypoxic events makes this even worse.

These studies suggest a mechanism where hypoxia can lead to death in any infant. Hypoxia occurs commonly in infants⁹⁸. The infant responds to hypoxia by decreasing oxygen consumption and metabolic rate^{88,89,90,91}. Decreased metabolic rate decreases CO₂ production, and thus decreases central ventilatory drive. Decreased central ventilatory drive decreases minute ventilation. Decreased minute ventilation may result in apnea or respiratory failure. Decreased minute ventilation, apnea, and respiratory failure can all cause more hypoxia, which perpetuates the cycle¹⁰¹. Thus, hypoxia may cause infants to enter a pattern of maladaptive physiologic responses which can result in death.

HOW ARE WE TO UNDERSTAND SIDS?

Much of SIDS research has searched for a single abnormality or disorder in a single physiological system. The idea that some infants might be vulnerable to SIDS, and others not, based on a pre-existing abnormality, has not been a productive research strategy. If SIDS were as simple as one abnormality in one physiologic system, the major research thrust directed toward solving the mystery of SIDS would likely be closer to answering the question by now. Thus, SIDS must be more complex than a single abnormality in a single physiologic system. Further, there is no evidence of serious disease or injury found at autopsy in SIDS victims, suggesting that these infants have an increased vulnerability to phenomena which occur frequently in normal infants.

In order to better focus SIDS research, Mortola suggested we imagine a car attempting to drive up a steep mountain road¹⁰¹. The car has stopped, and can not go up the hill. Perhaps all four tires are flat. If one changes the tires, the car could continue to go up the hill. This is the traditional medical model of disease. One identifies a problem and finds a solution. SIDS research has followed this model for the past 2-3 decades, yet this approach has not identified the cause of SIDS. Another possibility is that the car does not go up the hill, yet the tires are inflated, the engine is running, and there are no apparent problems with the car. Perhaps the car does not go up the hill because there are too many passengers, the engine is not powerful enough, the road is too rocky, or the road is too steep. In this view, the car does not go up the hill because of intrinsic characteristics of the car and/or circumstances, not because of a problem which can be fixed. It is, perhaps, this second view which will more accurately reflect the nature of SIDS.

SIDS may be an interaction between intrinsic characteristics of the infant and circumstances. This does not necessarily imply that a distinct *abnormality* exists in SIDS infants. Rather, SIDS may occur in infants without definitive abnormalities, due to intrinsic characteristics of infant physiology, developmental influences, and circumstance SIDS is more properly viewed as a dynamic interaction of many factors, which are constantly changing, and which together dictate the infant's chances of dying from SIDS. This fundamentally changes the way we view SIDS, and what now becomes important is the interaction of at least three factors.

- 1) **Development:** SIDS is most common between the ages of 2-4 months. Thus, all infants may face a developmental window of increased vulnerability for SIDS during this age. It might take less of an environmental stress to trigger SIDS in an infant during this age than if the infant was younger or older.
- 2) **Infant Physiologic Responses:** All infants have physiologic responses to various stresses or challenges. For example, infants increase breathing in response to low oxygen. However, some infants will increase breathing more than other infants. Infants increase heart rate in response to exercise or work. However, some infants will increase heart rate more than other infants. Although all infants have these responses, the magnitude of these responses differs between infants. Those infants with brisker responses may be able to tolerate greater environmental stresses or challenges than those with lesser responses, or vice versa. These differences in some responses may mean that all infants are vulnerable to SIDS, but some infants are more vulnerable than others.
- 3) **Environmental Factors:** Infants are constantly challenged by changes in their environment to which they must respond. For some infants, prone sleeping may cause sufficient compromise that SIDS can occur, especially if it occurs during the 2-4 month age in an infant with more "vulnerable" physiologic responsiveness. For other infants, prone sleeping may pose little danger, especially over 6-months of age. Respiratory infections, overheating, cigarette smoke, soft bedding, and other stresses are variable environmental challenges which may trigger SIDS in some infants, but not in others.

Thus, SIDS is likely to be a multifactorial problem requiring the dynamic interaction of many components to cause death. For example, SIDS may start with a more vulnerable infant with subtle decreases in physiologic responses. Then, the infant may need to be at an age when infants are increasingly vulnerable, such as three months of age when the respiratory system is unstable in all infants. Then, SIDS may require an environmental trigger, such as an upper respiratory infection. Sleeping position may be an additional contributing factor to such an infant, even if it makes no difference to breathing in an otherwise healthy infant at a younger or older age.

If SIDS causes death through respiratory mechanisms in infants with robust physiology, who breathe regularly and control oxygenation precisely, then SIDS would have to be a catastrophic event to move from regular respirations and consistent oxygenation to death. Results from home recordings of respiratory inductance plethysmography, ECG, and pulse oximetry suggest that the normal infant's control of ventilation and oxygenation is not precise⁹⁸. Normal infants commonly have prolonged central, obstructive, or mixed apneas up to 20-seconds duration in the home. In addition, normal infants commonly have spontaneous arterial oxygen desaturations during periodic breathing to the low 80% range, and occasional infants will spontaneously desaturate to the low 70% range⁹⁸. Prolonged obstructive apneas were recorded in a few normal infants with simple upper respiratory infections. If infants have such spontaneous events frequently, then SIDS may not have to be such a catastrophic event. A less severe event might be sufficient to cause death in an infant who already has frequent apneas and/or desaturations during sleep.

Is there any evidence that infants who die suddenly are profoundly hypoxic prior to death? Poets and associates analyzed recordings from nine infants on home apnea-bradycardia monitors, who died suddenly¹⁴⁷. The monitor alarm which triggered the recording and audible alarm was low heart rate, not apnea¹⁴⁷. However, these infants also showed a breathing pattern most consistent with gasping, which only occurs in the presence of profound hypoxia ($P_{aO_2} < 15-20$ torr)¹⁴⁷. This indicates, that at least for these infants, they were profoundly hypoxia just prior to death, consistent with this theory.

It is likely that SIDS represents a series of events, modified by the above factors, which are initiated by common events^{101,102}. All infants sleep. However, sleep is associated with respiratory abnormalities, even in normal infants. These respiratory abnormalities are modified by developmental immaturity of the respiratory system in infants; and they include irregular breathing (central respiratory pauses), obstructive apneas, and resultant hypoxia and CO₂ retention. The infant responds to hypoxia by decreasing its oxygen requirement or metabolic rate. When the oxygen demand is decreased, the central drive to breathe also decreases. Therefore, ventilation decreases in response to hypoxia, which results in worse hypoxia, which eventually causes cessation of breathing (apnea) or respiratory failure. In order to prevent death, the infant must rescue himself from these hypoxic respiratory sequelae. Arousal from sleep is one protective physiologic response to hypoxia. However, recurrent hypoxia blunts this arousal response^{74,81}. Further, the hypoxic arousal response naturally decreases at 2-months of age⁷⁵, which begins the peak incidence of SIDS. Thus, infants in the peak age range for SIDS, and those exposed to repetitive hypoxia, may have blunted arousal responses to hypoxia^{65,74,75,81}. If arousal fails to revive the infant, then gasping (auto-resuscitation) must be used. Gasping is the last protective response to reinstate breathing^{92,93,147}. However, gasping is also inhibited in infants. Infants with hypoxia or respiratory failure, without effective arousal or gasping responses, may die from SIDS.

SUMMARY OF RESEARCH INTO CAUSES OF SIDS

There is a great deal of evidence pointing to respiratory dysfunction and hypoxia as important mechanisms of death in SIDS. The search for specific abnormalities in the respiratory system, which might cause SIDS, has not been fruitful. However, all infants have vulnerability to hypoxia and respiratory dysfunction, and have inadequate protective physiologic responses to defend against common stresses. Thus, all infants may share vulnerability for SIDS, and there

are numerous respiratory and hypoxic mechanisms which can occur in nearly every infant, which can cause death. The current conceptual model of SIDS is not a single abnormality in a single physiologic system, but rather a dynamic interaction of factors which come together to cause SIDS. SIDS may be initiated by common events, such as respiratory dysfunction during sleep. Normal infants have had prolonged apneas and desaturations recorded at home. Infants may not have to be *abnormal* to initiate SIDS. Respiratory dysfunction leads to hypoxia. Hypoxia decreases metabolic rate in infants, which, in turn, depresses ventilation, causing more hypoxia. Repetitive hypoxia and age may inhibit protective physiologic responses, such as arousal or gasping. Hypoxic depression of ventilation worsens hypoxia, which may proceed to apnea, respiratory failure, and death. The hypoxic depression of metabolic rate may prevent resuscitation of SIDS infants, even if ventilation and circulation are transiently restored.

We have focused on physiologic mechanisms and hypoxic responses, present in every infant, which can proceed to SIDS. But, we must return to the fact that 999 out of 1,000 infants survive these maladaptive mechanisms. Future research must attempt to understand why only a few infants die from these mechanisms while most survive.

POTENTIALLY MODIFIABLE RISK FACTORS

Early epidemiologic studies defined a number of risk factors which were characteristics of infants who died from SIDS⁷. In general, these were not modifiable risk factors. It was hoped that these might be used to identify infants at high risk prior to death, so that potentially preventive interventions could be concentrated on those babies. However, no such *markers* emerged. Since 1985, investigators from around the world began to identify risk factors which could be changed, and thus might modify an infant's risk for SIDS⁵. However, it must be remembered that risk factors are not *causes* of SIDS, but some may be *clues* to understanding the cause of SIDS⁵.

INFANT SLEEPING POSITION

Prone sleeping (sleeping on the stomach) was not common until the middle of the twentieth century. It then became fashionable, although the reasons for the popularity of prone sleeping in infants are not clear. However, after sufficient numbers of babies routinely slept prone (50%-70%), some investigators began to suspect that prone sleeping carried a higher risk of dying from SIDS than side or back sleeping [Table 2]^{103,104,105,106,107,108,109,110,111,112,113,114}.

In response to these reports, some countries, notably Australia, England, Norway, and the Netherlands, initiated public education campaigns designed to change the infant sleeping position from prone to supine in order to reduce the SIDS rate^{115,116}. Dramatic decreases in SIDS rates, often as much as 50%, were observed in response to these campaigns^{115,116,117,118}. However, there was fear that supine sleeping might increase the dangers of aspiration. Countries which increased supine sleeping did not experience an increased incidence of aspiration. Thus, otherwise healthy infants can handle any secretions or vomitus without aspiration, regardless of their sleeping position. In April, 1992, the *American Academy of Pediatrics* recommended that healthy infants be encouraged to sleep on their backs because of evidence that it might reduce the risk of SIDS in infants. In 1994, the *Back to Sleep* campaign was officially launched in the U.S. by the American Academy of Pediatrics, SIDS Alliance, and National Institute of Child Health

Table 2: SLEEPING POSITION OF SIDS VICTIMS AND CONTROLS

Year	Authors	SIDS	Controls	Sleeping Position	Odds Ratio (95% C.I.)	P
1970	Froggatt	148	148	Not supine	4.2 (2.3-7.8)	<0.01
1972	Carpenter	110	110	Not supine	2.3 (1.3-4.3)	<0.05
1986	Cameron	208	393	Prone	3.2 (2.2-4.5)	<0.01
1986	McGlashan	164	329	Prone	1.9 (1.3-2.8)	<0.05
1987	Senecal	20	318	Prone	12.7 (3.6-44.2)	<0.01
1988	Beal	100	156	Prone	9.3 (4.9-17.6)	<0.01
1988	Nicholl	265	273	Prone	2.2 (1.5-3.1)	<0.01
1989	Lee	16	32	Prone	11.7 (2.1-66.4)	<0.01
1989	Jonge	62	254	Prone	4.9 (2.3-10.3)	<0.01
1990	Fleming	67	134	Prone	8.8 (3.4-23.8)	<0.01
1991	Mitchell	128	503	Prone	5.7 (3.3-10.1)	<0.01
1991	Dwyer	15	116	Prone	4.5 (1.3-15.4)	<0.01
1992	Wigfield	32	64	Prone	9.1 (3.4-24.8)	<0.01

P.J. Fleming Understanding SIDS risk factors: The Avon population based studies of epidemiology and physiology *Proceedings of the 12th Conference on Apnea of Infancy*, 1994.

And Human Development. From 1992 to 1996 in the U.S., prone sleeping fell from 70% of infants to 24% of infants, and the SIDS rate fell from 1.20/1000 to 0.82/1000 [Table 3]¹¹⁹. There has been a 32% decrease in the SIDS rate in the U.S. between 1990 and 1996 [Tables 1 and 3]¹¹⁹. Other countries report decreases in SIDS in excess of 50%, and these appear to be most closely correlated with the elimination of prone sleeping^{115,116,117}. **Thus, otherwise healthy infants should be encouraged to sleep on their backs.**

Table 3: INFANT SLEEPING POSITION AND SIDS IN THE U.S.A.¹¹⁹

Year	Prone	Side	Back	SIDS Rate
1992	70%	15%	13%	1.20
1993	58%	22%	17%	1.17
1994	43%	27%	27%	1.03
1995	29%	32%	38%	0.84
1996	24%	39%	35%	0.82

Sleeping on the side is associated with an increased risk of SIDS compared to supine sleeping, though not as great as prone sleeping [Table 4]. The increased risk of side sleeping may be related to it being the least stable sleeping position in infants. Therefore, they roll from the side onto the prone position, increasing the risk. Thus, *Back to Sleep* or *Reduce the Risks* campaigns

should stress supine or back sleeping. Side sleeping should not be recommended to reduce the SIDS risk. Similarly, propping devices to keep the baby on the side are not recommended.

Table 4: RELATIVE SIDS RISK OF PRONE AND SIDE SLEEPING

Author	Location	Year	Prone Sleeping Odds Ratio	Side Sleeping Odds Ratio
Oyen	Norway	1992-95	16.5 (9.3-29.0)	3.7 (2.1-6.3)
Fleming	United Kingdom	1993-95	21.4 (11.7-39.1)	4.5 (2.7-7.7)

Proceedings of the Fourth SIDS International Conference, 1996.

Infants who usually sleep on their backs are at markedly increased risk of dying from SIDS if they are placed in the prone position to sleep¹²⁰. Mitchell and coworkers studied 485 SIDS that occurred in New Zealand 1987-1990, and compared them to 18,900 control infants¹²⁰. Infants who usually sleep nonprone and were last placed nonprone had lowest risk (OR 1.0). Infants who usually sleep prone, and who were last placed prone had an increased risk for SIDS (OR 4.6 [95% CI: 3.4-6.3]). Infants who usually sleep non-prone, but who were last placed prone ("unaccustomed to prone sleep") had the highest SIDS risk (OR 19.3 [95% CI: 8.2-44.8]). This group accounted for 8% of all SIDS. In this study, 20% of all SIDS involved lack of experience with prone sleeping. Mitchell's study suggests "the possibility that an infant's competence in escaping from potentially lethal situations during prone sleep (i.e., face down position) may be impaired by inexperience with prone sleeping"¹²⁰. The reason why infants who routinely sleep supine may be at more risk when placed prone is because they have not had the opportunity to practice motor skills and behaviors which permit them to raise and turn their heads to avoid the face down sleeping position. Thus, unaccustomed prone sleeping is an even more perilous situation than usual prone sleeping, though both are associated with an increased risk compared to supine sleeping.

If supine sleeping is associated with a decreased SIDS risk, why don't all babies sleep on their backs? Willinger¹¹⁹, Lesko¹²¹, and Brenner¹²² surveyed U.S. households about their infant sleeping practices. They found a number of predictors of prone sleeping [Table 5]. For example, African-American infants were 2.3-times more likely to sleep prone^{119,121,122}. They had a higher incidence of prone sleeping [82% in 1992; 43% in 1996], and a higher SIDS rate [2.2 per 1,000 in 1992; 1.6 per 1,000 in 1996]¹¹⁹. Further, many infants, who did not sleep prone at age 1-month, did sleep prone by age 3-months¹²¹. Factors which predict a shift to prone sleeping by age 3-months are African-American, Hispanic, young mothers, increased parity, and male infant¹²¹. Thus, educational campaigns to encourage supine sleeping should be directed especially toward African-American infants, poor families, single mothers, young mothers, poorly educated mothers, and other groups where prone sleeping remains common. Prone sleeping remains higher in child care settings as well.

How might sleeping prone increase the risk for SIDS? The mechanism by which prone sleeping increases the risk for SIDS is not known. However, there are a number of possible mechanisms, including overheating, direct nasal occlusion, vertebral artery compression, rebreathing, and decreased arousal^{123,124,125}. Research is ongoing to understand how risk factors, such as sleeping position, might increase the risk for SIDS.

Table 5: PREDICTORS OF PRONE SLEEPING IN INFANTS

Odd ratio for Prone Sleeping	Willinger et al ¹¹⁹	Lesko et al ¹²¹	Brenner et al ¹²²
African American	2.34 [CI 1.68-3.26]	2.1 [CI 1.7-2.6]	2.37 [CI 1.25-4.50]
Hispanic	0.73 [CI 0.50-1.07]	2.2 [CI 1.8-2.8]	0.72 [CI 0.41-1.25]
Maternal Age (20-29 years)	1.28 [CI 1.09-1.50]	1.4 [CI 1.1-1.7]	---
Maternal Age <20 years	1.09 [CI 0.72-1.66]	1.5 [CI 1.0-2.03]	2.07 [CI 1.34-3.52]
Poverty	---	---	1.78 [CI 1.12-2.83]
Single Mother	---	---	2.17 [CI 1.34-3.52]
Maternal Education <12 years	1.17 [CI 0.81-1.69]	1.2 [CI 1.0-1.5]	1.57 [CI 1.04-2.37]
Male Infant	1.14 [CI 0.98-1.32]	1.2 [CI 1.1-1.4]	---
Infant <8 weeks of age	0.63 [CI 0.46-0.85]	---	---
Mother had a Previous Child	1.68 [CI 1.43-1.97]	1.8 [CI 1.4-2.1]	0.83 [CI 0.54-1.28]
Grandmother at Home	---	---	1.88 [CI 1.20-2.94]

Although healthy babies should sleep on their backs, many babies have died from SIDS while sleeping on their backs, and most infants who sleep on their stomachs will not die from SIDS. Thus, the prone position does not always result in SIDS, and sleeping supine does not totally prevent SIDS. Factors other than sleeping position remain important in the cause of SIDS.

CIGARETTE SMOKING

Cigarette smoking has been associated with an increased risk for SIDS in many studies ^{5,126,127,128,129,130,131,132}. Maternal cigarette smoking during pregnancy and after pregnancy increases the SIDS risk proportionate to the number of cigarettes smoked [Table 6] ¹³¹. Neither mother nor father should smoke cigarettes during or after pregnancy. The infant, once born, should be kept in a "smoke-free zone." However, many babies have died from SIDS with parents who never smoked cigarettes, and most infants of smoking parents will not die from SIDS. Thus, parental cigarette smoking does not always result in SIDS, and not smoking does not totally prevent SIDS. Factors other than cigarette smoking, remain important in the cause of SIDS.

SIDS researchers are trying to understand how risk factors, such as sleeping position and parental cigarette smoking, might increase the risk for SIDS. Franco and coworkers found that the intensity of an auditory challenge required to cause arousal in infants was increased in those exposed to prenatal cigarette smoking, compared to those who were not ⁸⁴. Since prenatal cigarette smoking is also associated with an increased risk for SIDS, blunted arousal responses may be important contributors to SIDS. This study, and others like it, may provide a physiologic explanation for the increased SIDS risk associated with some potentially modifiable risk factors.

Table 6: CIGARETTE SMOKING AND SIDS.

Author	Location	Year	Risk Factor	Odds Ratio (95% Conf)
Fleming	United Kingdom	1993-95	Maternal Smoking During Pregnancy	4.84 (3.33-7.04)
			1-9 cigarettes/day	4.59
			10-19 cigarettes/day	5.38
			20+ cigarettes/day	7.88
Schellscheidt	Norway	1990-94	Maternal Smoking	
			1-9 cigarettes/day >10 cigarettes/day	2.4 (1.7-5.4) 7.2 (5.3-9.7)
Schellscheidt	Norway	1990-94	Mother >10 cigarettes/day	
			Preterm Infants (<37 wks) Term Infants (39-40 wks)	15.6 (6.4-39.2) 5.3 (3.1-9.1)
Alm	Norway	1992-95	Maternal Smoking	
			Before Pregnancy	2.63
			During Pregnancy After Pregnancy	3.60 3.25
Kohlendorfer	Austria	1984-94	Maternal Smoking During Pregnancy	2.2 (1.0-4.5)
Fleming	United Kingdom	1993-95	Paternal Smoking After Pregnancy	2.92 (1.60-5.34)
Alm	Norway	1992-95	Paternal Smoking	
			Before Pregnancy	1.20
			During Pregnancy After Pregnancy	1.64 2.12
Fleming	United Kingdom	1993-95	Infant Exposure to Smoke	
			1-2 hours/day	2.02 (1.18-3.36)
			3-5 hours/day	3.41 (1.85-6.12)
			6-8 hours/day >8 hours/day	7.36 (3.49-15.47) 9.49 (5.19-17.40)

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OTHER POTENTIALLY MODIFIABLE RISK FACTORS

Maternal illicit substance abuse has been shown to increase the SIDS rate approximately 8-10 times that of the general population ⁶. Cocaine use is associated with an 8-times increased risk and opiate use with a 20-times increased risk ⁶. Fleming and colleagues showed that many factors in the infant's sleeping environment after birth may be associated with variable risks for SIDS [Table 7] ¹¹⁸.

For centuries, there has been concern that when the mother and baby sleep together, the mother may roll over onto the baby, causing suffocation¹³². This is not commonly seen, but is possible when parents are obtunded to an infant's struggling under them (drugs, alcohol, etc)¹³².

Table 7: FACTORS IN SLEEPING ENVIRONMENT AND SIDS RISK¹¹⁸

Factors in Sleeping Environment	Odds Ratio (95% conf)
Prone Sleeping	10.0 (4.3-23.2)
Side Sleeping	2.2 (1.4-3.4)
Covers Over Infant's Head	31.4 (10.4-95.0)
Tog Value >10 (Over-bundling)	1.0 (0.4-2.5)
Wearing Hat	6.2 (0.7-51.9)
Heating on All Night	3.1 (1.6-6.2)
If Mother Ever Breast-Fed	0.4 (0.3-0.7)
Bed Sharing with Parents all Night	4.1 (1.8-9.2)
Using Pacifier	0.4 (0.3-0.7)
Using Duvet (Quilt)	1.9 (1.1-3.1)
Loose Bed Coverings	1.3 (0.8-2.0)

Bedsharing with the infant and parents (or co-sleeping) has been shown to be a risk factor for SIDS when parents smoke cigarettes¹³². Bedsharing in lower socio-economic conditions, where the entire family sleeps in one bed, soft mattress, cigarette smoking, etc., may be a dangerous and high risk situation^{132,133}. On the other hand, it has also been suggested that bedsharing may reduce the risk for SIDS^{134,135,136}. Bedsharing which occurs in an optimal setting is probably not a risk factor for SIDS^{133,134,135,136}. Bedsharing promotes breast feeding, which may offer some protection¹³⁵. There is significant interaction between the mother and baby during bedsharing^{136,137}. The mother and baby tend to wake and sleep together^{136,137}. It has been hypothesized that the mother may wake the baby throughout the night, which may be protective from SIDS by increasing arousal^{136,137}. However, one study suggested the baby tended to wake the mother, rather than the mother causing possibly protective arousals in the baby¹³⁷. There were no potentially dangerous situations observed (i.e., overlaying)^{136,137}. When bed-sharing is done voluntarily, and not as a result of overcrowding, it is probably not associated with an increased SIDS risk. However, there is yet no scientific evidence that it is protective either.

Infants who breastfeed have been shown to have a lower risk of SIDS¹¹⁸. However, careful analyses of the data indicate that breastfeeding is associated with other epidemiologic factors which reduce the risk of SIDS, and that breastfeeding *per se* is probably not protective against SIDS¹¹⁸. While there are many general health reasons to encourage breastfeeding, it probably does not decrease an infant's risk for SIDS.

The most current information provides at least some evidence that each of the following recommendations may be associated with some reduction in SIDS risk:

1. Put your baby to sleep on the back (supine).
2. Side sleeping is now associated with a higher risk than supine, though not as high as prone. Do not use wedges to constrain a baby's movement.
3. Keep your baby in a cigarette smoke-free environment.
4. Neither mother nor father should smoke cigarettes during pregnancy.
5. Breastfeed your baby.
6. Do not let your baby get too hot.
7. Have your baby on a firm mattress without pillows, toys, or soft bedding under the baby.
8. Do not bed-share with your baby if you smoke cigarettes.

Can SIDS be prevented? SIDS can not be entirely prevented at present. However, decreases in SIDS rates were observed in response to public education campaigns which decreased potentially modifiable risk factors for SIDS. A goal of SIDS research is to prevent SIDS. Although we can not totally prevent SIDS at present, decreasing potentially modifiable risk factors may be able to reduce the risk for SIDS in some settings.

More research is needed on the possible mechanisms of potentially modifiable risk factors in SIDS. While it is not likely that a better understanding of potentially modifiable risk factors will totally explain the cause of SIDS, it is possible that such research may add important clues to our understanding of SIDS. Therefore, this research should be encouraged.

Since SIDS is not caused by these potentially modifiable risk factors, it is important to emphasize that SIDS parents did not *cause* their babies to die, even if their infants were exposed to these risk factors. Their infants might still have died. Based on current knowledge, there is nothing that SIDS parents did to cause their babies' deaths, and nothing they could have done to prevent them.

SIDS AND GRIEF

The parents and families of a SIDS victim are no less the victims of this tragedy than their babies^{2,138,139}. Although the death of any child is painful, SIDS deaths have some unique characteristics. SIDS deaths are unexpected, so parents have not had the opportunity to plan the death or say to "good-bye" to their child. Perhaps the most important issue is that, at the present time, SIDS deaths are unexplained. Medical professionals can not tell parents how their babies died. Thus, parents search the pregnancy and child's life for things that they did, or did not do, which might have caused the death. The guilt generated by a SIDS death in the parents is tremendous, and is generally more than in other infant deaths where the cause is unknown.

For most families of SIDS victims, the single best and most important resource is a SIDS Parent Support Group^{2,138,139}. The *Sudden Infant Death Syndrome Alliance* is a national SIDS parent support organization, which has parent support counselors who are available to speak with SIDS parents at any time. While the immediate impact of the SIDS death is devastating to families, the ability to talk with someone who has been through it, who understands it, and who has survived, it is reassuring. SIDS parent support groups are the best resource available to SIDS parents, and it is extremely important to get new SIDS parents in touch with their local organization as soon as possible after the death.

When dealing with families of SIDS victims, the role of the health professional is to educate the family about SIDS and to reassure them that they did not cause the death of their baby, either by something they did or by something they did not do. It is important to emphasize that SIDS can not be prevented, and there is nothing they or anyone else could have done to prevent their child's death. Many families of SIDS victims report that they are reassured to hear this from a health professional (an expert).

SUBSEQUENT SIBLINGS OF SUDDEN INFANT DEATH SYNDROME VICTIMS

Sudden infant death syndrome (SIDS) is not thought to be hereditary. However, subsequent siblings of SIDS victims may be at increased risk of dying from SIDS^{53,69,70,71,72,140,141,142,143}. This statement is based on nine studies [Table 8]. However, these current studies are not perfect. Two lines of evidence suggest that the SIDS recurrence risk for the subsequent sibling of one previous SIDS victim is *at or near that* of the general population.

- 1) Peterson and colleagues showed that the risk for SIDS siblings is no greater than for infants born to non-SIDS parents of similar age, birth order, etc.⁷⁰. However, Guntheroth showed that SIDS rates were elevated in SIDS siblings, and that the infant death rate from all causes (both SIDS and non-SIDS) was 2%⁷². However, this was similar to the infant death rate for siblings of infants dying from causes other than SIDS⁷². Thus, a family history of SIDS *per se* does not seem to confer a substantially increased risk over infants born into *similar* non-SIDS families^{70,72}.
- 2) There are sub-groups of SIDS siblings who have an increased risk of SIDS, above and beyond that of the group of siblings of one previous SIDS victim^{9,10,11,141}. These include siblings of two-or-more previous SIDS victims, surviving twin siblings of SIDS victims, and SIDS siblings with serious apnea^{9,10,11,144}. This suggests the possibility that the increased risk for SIDS attributed to all SIDS siblings may be skewed by a small number of very high risk infants. The risk for SIDS siblings outside these sub-groups may be normal.

Thus, the SIDS recurrence risk for subsequent siblings of one previous SIDS victim is probably not increased over the SIDS risk for the general population.

Because the SIDS recurrence risk for subsequent siblings of one previous SIDS victim is not markedly increased, current recommendations are that SIDS siblings do not require study or treatment^{66,145}. Home apnea-bradycardia monitoring has not been shown to reduce or not reduce the SIDS recurrence risk in SIDS siblings⁶⁶. The SIDS rates for SIDS siblings managed with home apnea-bradycardia monitoring are similar to those where monitoring was not used^{53,146}. However, some SIDS parents may be sufficiently anxious about their subsequent child that home apnea-bradycardia monitoring will reduce anxiety and improve parenting skills. This is an acceptable indication for the use of home apnea-bradycardia monitoring^{66,145}. On the other hand, parents of SIDS siblings, who do not wish to use home apnea-bradycardia monitoring, should not be forced to do so, based on the absence of scientific information supporting its efficacy.

Table 8: RISK OF SIDS IN SUBSEQUENT SIBLINGS OF SIDS VICTIMS.

Author	Year	Location	Total	SIDS Deaths	SIDS Rate*	Relative Risk **
Adelson ¹⁴⁰	1956	Ohio, USA	126	2	15.9	5-8
Froggatt ¹⁴¹	1971	Northern Ireland	360	5	13.9 (2.8-36.4)	4.6
Peterson ¹⁴²	1980	United States	839	18	21.5 (9.5-34.7)	10.8
Beal ¹⁴³	1983	South Australia	302	8	19.9 (7.3-43.4)	10.0
Irgens ⁶⁹	1984	Norway	1043	5	4.8 (1.5-11.2)	3.7
Peterson ⁷⁰	1986	Washington, USA	810	6	7.4 (3.5-17.8)	3.4
Ward ⁵³	1986	California USA	371	3	2.7 (0.3-15.2)	1.7
Beal ⁷¹	1988	South Australia	660	14	21.2 (9.5-33.0)	10.1
Guntheroth ⁷²	1990	Oregon, USA	385	5	13.1 (4.4-27.9)	6.0

* SIDS Rate is SIDS deaths per 1000 SIDS siblings.

() 95% Confidence Limits of SIDS Recurrence Rates.

** Relative Risk = SIDS rate for SIDS siblings/SIDS rate for controls.

SUMMARY

Sudden infant death syndrome (SIDS) is the most common cause of death between the ages of 1-month and 1-year. It affects nearly one out of every 1,000 live births. The etiology of SIDS is unknown. There are no tests currently available which predict the infant who will die from SIDS. Although reduction of SIDS risks for populations may be possible, SIDS deaths can not be prevented in individual infants.

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