The sudden infant death syndrome (SIDS), which is characterized by the sudden death of a seemingly healthy infant during a sleep period, has long been considered one of the most mysterious disorders in medicine. However, in recent years, SIDS has been substantially demystified by major advances in our understanding of its relationship to sleep and homeostasis, environmental and genetic risk factors, and biochemical and molecular abnormalities. The most important advance has been the discovery that the prone sleep position more than triples the risk of SIDS, which in the early 1990s led to national and international campaigns advocating a supine sleep position for infants. Since then, it has been estimated that rates of SIDS have declined by more than 50%, and thousands of infant lives have been saved. However, SIDS still remains the leading cause of post-neonatal infant death in the United States and is the third leading cause of infant mortality overall. This review highlights the major advances in our understanding of SIDS.
among Maoris in New Zealand; and among aboriginal Australians. In a recent review of SIDS data from 13 predominantly industrialized countries, the majority of countries had a major decrease in SIDS rates from 1990 to 2005 (the most recent year for which data were available), with the largest decreases occurring before 2000. These decreases ranged from 40% in Argentina to 83% in Ireland. The true incidence of SIDS may be masked by a so-called diagnostic shift, or the use of diagnoses other than SIDS on death certificates (e.g., accidental suffocation, positional accidental asphyxia, and indeterminate cause). Diagnostic shift may explain, in part, why postneonatal death rates for both SIDS and non-SIDS have remained static since approximately 2000.

The term “sudden and unexpected infant death” (SUID) is used to describe all such deaths, regardless of cause. Cases of SUID that remain unexplained after a complete autopsy and review of the circumstances of death and clinical history are classified as SIDS. Thus, SIDS is one of the causes of SUID and accounts for 80% of such deaths. Approximately 20% of SUID cases have a clear cause, including severe, unequivocal infection. In the past 25 years, two causes of death have been defined in a small but important percentage of the SUID population. These are inherited disorders of fatty acid oxidation, particularly mutations in the medium-chain acyl-coenzyme A dehydrogenase (MCAD) gene (accounting for approximately 1% of SUID cases), and genetic cardiac channelopathies (accounting for 5 to 10% of SUID cases). In these disorders, metabolic or molecular testing in combination with autopsy provides the specific diagnosis. Some investigators have suggested that once a specific cause is identified, such cases should no longer be classified as either SIDS or SUID but, rather, as explained deaths.

It is estimated that among cases of sudden infant death, the incidence of infanticide due to intentional suffocation is less than 5%. Although intentional suffocation with a soft object (e.g., a pillow) is virtually impossible to distinguish from SIDS at autopsy, the likelihood of such a cause may be suggested by the death of an infant over the age of 6 months, a history of recurrent life-threatening events in the infant under the care of the same person, and a history of a previous death of an infant with the same caretaker.

A causal role for mild infection in sudden infant death is suggested by reports that in approximately half of SIDS cases, the infants have a seemingly trivial infection around the time of death, as well as mild tracheobronchial inflammation and altered serum immunoglobulin or cytokine levels and the presence of microbial isolates at autopsy. In infants who die unexpectedly of infection, the given organism may precipitate a lethal cytokine cascade or toxic response. If all specific causes of infant death are delineated, the designations SUID and SIDS will no longer be needed.

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<th>Newer Models for SIDS</th>
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<td>After the recognition that sleeping in the prone position was associated with SIDS, attention turned to factors that might trigger infant death in this position. Such factors include asphyxia due to airway compression or rebreathing of exhaled gases in the face-down position, impaired heat loss with subsequent hyperthermia when the face is pressed against bedding, impaired cardiorespiratory regulation related to heat stress, and compromised arousal in response to asphyxia generated in the prone position. One way of conceptualizing the emerging multidisciplinary data is with the Triple-Risk Model, proposed in 1994. Like other models, it emphasizes the interaction of multiple factors in the pathogenesis of SIDS. According to this model, SIDS occurs when three factors are present simultaneously. The first factor is an underlying vulnerability in the infant; the second, a critical developmental period; and the third, an exogenous stressor (Table 1). Exogenous stressors are considered to be homeostatic stressors, such as asphyxia. During the first year of life, rapid changes in the maturation of cardiorespiratory control and in cycling between sleeping and waking occur, first as the fetus transitions to extrauterine life and subsequently as the infant adjusts to postnatal life. According to the Triple-Risk Model, SIDS does not cause death in normal infants but, rather, only in vulnerable infants with an underlying abnormality. Therefore, the change to a supine sleep position is effective because once the exogenous stressor (e.g., face-down position) is...</td>
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removed, the vulnerable infant passes through the critical period unharmed. However, otherwise normal infants without innate vulnerability may also die if they are caught in situations from which they cannot escape — for example, if they become wedged between the mattress and the crib railing.\textsuperscript{31} Bed sharing may involve compromise of an infant’s upper airway due to close bodily contact with another person or suffocation by adult bedding, such as pillows.\textsuperscript{31} In a recent study, 85% of 209 sudden infant deaths were associated with circumstances “consistent with asphyxia,” which included a prone position and bed sharing, suggesting a major role of asphyxia in the pathogenesis of sudden infant death overall.\textsuperscript{32} Careful investigation after the occurrence of sudden infant deaths has indicated that approximately 13% or more of such unexplained deaths are attributable to accidental or intentional suffocation.\textsuperscript{33} Nevertheless, the diagnosis of asphyxia as the cause of death is subjective, since terminal blood gas levels are obviously unknown. There are no biomarkers that can be obtained posthumously that distinguish between asphyxia-related deaths in normal infants and those in vulnerable infants.

**Risk Factors for SIDS**

Risk factors for SIDS can be divided into extrinsic and intrinsic categories.\textsuperscript{34} Extrinsic risk factors are physical stressors that would place a vulnerable infant at risk for asphyxia or other homeostatic derangement. Such extrinsic factors include prone and side-sleeping positions, bedclothes that cover the head, sleeping on sofas or other soft furniture in which the infant could become wedged, a high ambient temperature in the sleeping environment, soft bedding, and bed sharing.\textsuperscript{3,4,12,13,35,36} Although the incidence of a prone sleep position is currently 20% or less,\textsuperscript{16,37} 30 to 50% of infants with SIDS are still found in the prone position.\textsuperscript{38} Approximately 50% of sudden infant deaths occur when infants are sharing a bed, sofa, or sofa chair with another person.\textsuperscript{13} The prone sleep position and a soft mattress are associated with an increase by a factor of 20 in the risk of SIDS, suggesting additive risk for these two factors.\textsuperscript{36} However, there are arguments in favor of bed sharing, which include facilitation of breastfeeding and nighttime bonding, behaviors that are beneficial to an infant’s well-being.\textsuperscript{39} Approximately 10% of SIDS cases occur in infants who sleep in a supine position and do not share a bed and whose face is not covered by bedclothes.\textsuperscript{5} This finding reinforces the points that such risk factors are not causative and that the causes of SIDS are multifactorial.

In addition to extrinsic risk factors related to external events around the time of death, intrinsic factors are postulated to affect the underlying vulnerability of the infant and thus increase the risk of SIDS. Intrinsic risk factors can be subdivided into developmental factors, such as prematurity,\textsuperscript{40} and putative genetic factors, such as familial SIDS (i.e., a recurrence of SIDS in subsequent siblings),\textsuperscript{25,41} male sex (by a 2:1 ratio), and race or ethnic group.\textsuperscript{13}

Certain genetic polymorphisms have been associated with SIDS.\textsuperscript{20,25,42,43} During the past two decades, the search for SIDS susceptibility genes has focused on the hypothesis that SIDS is a homeostatic disorder, and polymorphisms associated with SIDS have been reported in a variety of genes involved in autonomic function, neurotransmission, energy metabolism, and response to infection.\textsuperscript{25,42,43} In addition, the vulnerable infant’s response to environmental factors may actually reflect aberrant intrinsic responses. For that reason, events and environmental conditions extrinsic to the infant, such as poverty,\textsuperscript{5,15,44,45} adverse prenatal exposures to certain substances (e.g., cigarette smoke and alcohol or illicit drugs),\textsuperscript{6,12,46,47}

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**Table 1. Components of the Triple-Risk Model of the Sudden Infant Death Syndrome.**

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<tr>
<th>Intrinsic risk factors</th>
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<tr>
<td>Genetic</td>
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<td>Male sex</td>
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<tr>
<td>Polymorphism in the gene encoding the promoter region of the serotonin transporter</td>
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<tr>
<td>Black or Native American race or ethnic group</td>
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<tr>
<td>Developmental</td>
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<tr>
<td>Prematurity</td>
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<tr>
<td>Environmental</td>
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<tr>
<td>Perinatal exposure to smoking</td>
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<tr>
<td>Parental smoking, ethanol intake, or drug use</td>
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<tr>
<td>Socioeconomic disadvantage</td>
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<table>
<thead>
<tr>
<th>Extrinsic risk factors</th>
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<tr>
<td>Sleeping on the side or in prone position</td>
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<tr>
<td>Soft bedding</td>
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<tr>
<td>Bed sharing</td>
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<tr>
<td>Mild infections, including colds</td>
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and postnatal exposure to cigarette smoke, may trigger intrinsic responses in the vulnerable infant. For example, prenatal exposures to alcohol and cigarette smoke have a direct effect on neurotransmitter systems that are critical to homeostatic control in the developing human brain.48

Given the change in the demographic characteristics associated with SIDS, infants who die of SIDS in the present era may differ from those who died in previous eras. In the United Kingdom, for example, the proportion of SIDS deaths occurring in term infants has decreased, whereas the proportion in preterm infants has increased from 12% to 34% (P<0.001).46 Furthermore, the proportion of SIDS deaths occurring in families living in poverty has increased from 47% to 74% (P=0.003), and the proportion of SIDS deaths in infants of mothers who smoked during pregnancy has increased from 57% to 87% (P=0.004).46

The delineation of risk factors has been crucial for establishing the biologic basis of disparities in the incidence of SIDS among racial and ethnic groups.12,13,49 Although high SIDS rates among American blacks and Native Americans, Maoris, and aboriginal Australians may reflect factors that are independent of economic levels, poverty is associated with higher rates of maternal alcohol use and smoking during pregnancy, of prematurity, and of bed sharing (due to a lack of space and funds for cribs).12,16,49 Adding to the concern is evidence that recommendations for preventing SIDS are not reaching high-risk communities.13,15,37 Efforts are under way to understand the barriers to the promulgation of prevention messages and to optimize such recommendations in high-risk populations.6,13,50

**PUTATIVE TERMINAL PATHWAYS FOR SIDS**

A key question in SIDS research remains: How do infants die of SIDS? Although multiple theories have been advanced about the mechanism of death in SIDS, the cardiorespiratory-control hypothesis has dominated the research. In a 1982 review, Shannon and Kelly stated that “sudden death without an obvious cause implies the cessation of autonomic regulation of cardiovascular or respiratory activity or both.”20 In the ensuing years, all SIDS hypotheses essentially invoked defective respiratory or autonomic mechanisms.27,30,51-58 The roles of respiratory and autonomic pathways in SIDS are not mutually exclusive, given that infants who subsequently died of SIDS have frequently been found to have subclinical deficits in both respiratory and autonomic function.59-61 Ultimately, SIDS appears to involve failed defense mechanisms, with sleep in some important way unmasking the underlying vulnerability.

Clinical observations in infants, analysis of heart-rate and respiration recordings in infants who subsequently died of SIDS, and physiological studies in animal models provide compelling evidence for a respiratory pathway in the majority of SIDS deaths (Fig. 1). For purposes of clarity, the respiratory pathway to SIDS can be divided into five steps. First, a life-threatening event (which may occur in any infant during sleep) causes severe asphyxia, brain hypoperfusion, or both. Such life-threatening events include rebreathing of exhaled gases in the face-down position62 or in the face-covered (supine) position,63 reflex apnea originating from the laryngeal chemoreflex,64 and obstructive apnea due to gastric regurgitation. The laryngeal chemoreflex consists of reflex apnea and swallowing in response to the activation of receptors in the laryngeal lumen by water or gastric contents; it occurs early in life and disappears thereafter, although the precise time in infancy is unknown.64,65 Second, the vulnerable infant does not wake up and turn his or her head in response to asphyxia (combined hypoxia and hypercapnia), resulting in rebreathing or an inability to recover from apnea. Third, progressive asphyxia leads to a loss of consciousness and areflexia, a so-called hypoxic coma, a step that is hypothesized to occur on the basis of extrapolations from studies in animals that indicate the rapid development of coma when a critical level of the partial pressure of arterial oxygen is reached (approximately 10 mm Hg) or when hypoperfusion results in extreme brain hypoxia.66 Fourth, extreme bradycardia and hypoxic gasping ensue, changes that are evident in the terminal-event recordings in infants who were being monitored at home at the time of death from SIDS67,68 (Fig. 2). Fifth, in the vulnerable infant, autoresuscitation is impaired — a second defense failure — because of ineffective gasping, which results in uninterrupted apnea and death.67,68 Recordings in the same infants over time indicate that SIDS is not always a “sudden” disorder; rather, death may be preceded by a vicious cycle of episodic tachycardia, bradycardia, or apnea hours.
and even days before the lethal event. Evidence of intermittent hypoxia in infants with SIDS includes markers of chronic tissue hypoxia, such as brain-stem gliosis and apoptosis.

Arousal from sleep that is triggered by abnormal levels of carbon dioxide and oxygen is essential for the initiation of protective airway responses; indeed, head turning and escape to fresh air are critical for survival from an asphyxial micro-environment. Arousal involves a progressive activation of specific subcortical-to-cortical brain structures and consists of ascending and descending components that mediate cortical and subcortical arousal, respectively, with feedback loops between them. Cortical arousal involves noradrenergic, serotonergic (5-hydroxytryptamine), dopaminergic, cholinergic, and histaminergic neurons in the brain stem, basal forebrain, and hypothalamus, which excite the cerebral cortex and cause cortical activation. Subcortical arousal, on the other hand, is mediated mainly by brain-stem pathways that increase the heart rate, blood pressure, respiration, and postural tone without changes in cortical activity. In a prospective study of infants who subsequently died of SIDS, the infants had more frequent and longer episodes of subcortical arousal but fewer episodes of cortical arousal than did control infants, findings that are indicative of subclinical arousal deficits. Other prospective studies support the presence of arousal deficits in infants with SIDS.

In severe hypoxia or ischemia, normal breathing fails and is replaced by gasping. Gasping increases the volume of air in the lungs, followed by oxygen transport to the heart, increased cardiac output, and finally brain perfusion and re-oxygenation. The act of gasping involves neurons within the rostral medulla that demonstrate a “bursting” discharge due to pacemaker activity and that are modulated by 5-hydroxytryptamine and norepinephrine, which in combination sustain gasping and restore rhythmic respira-
In Panel A, the tracing starts with a gasp (G1), which is followed by a gradual increase in the heart rate (subpanel a). The spikes in heart rate that are simultaneous with gasps are probably reflecting artifacts. The second gasp (G2) results in an increased heart rate, at more than 100 beats per minute. After an interruption of 6 minutes 40 seconds, eupneic breaths are noted (subpanel b). Each large breath (B1–B6) is preceded and followed by smaller breaths. Larger breaths may be sighs. In Panel B, hyperpneic breaths (B1–B7) are followed by 35 seconds of primary apnea (hypoxic) apnea (subpanel a). Gasps (G1–G3) follow this apnea. G1 is an abnormally complex, triple gasp. A period of terminal gasps (G6–G8) occurs about 10 minutes after the onset of primary apnea, with decreasing amplitude and altered configuration (subpanel b). SIDS denotes sudden infant death syndrome.
all newborns obviously lack experience in sleeping in this position. Furthermore, infants have not fully learned the efficient protective strategies of head lifting and turning.\textsuperscript{58,91} Conceivably, developmental deficits in neural pathways that support reflexive motor learning may increase the risk associated with sleeping in the prone position. In addition, the prone sleep position is associated with impaired arousal from sleep, reduced vasomotor tone, and diminished laryngeal chemoreflexes and baroreceptor reflexes.\textsuperscript{92-95} Infants who were exposed to maternal smoking during gestation have reductions in the frequency of arousal from sleep.\textsuperscript{96}

**ASPHYXIA-RELATED SUDDEN DEATHS**

The search for the underlying vulnerability in SIDS infants has led to intense analysis of peripheral and central sites critical to protective responses to asphyxia and hypoxia. The major focus of SIDS research has been on the brain stem because it contains critical neural networks that mediate respiration, chemosensitivity, autonomic function, sleep, and arousal\textsuperscript{53,57} (Fig. 3). Abnormalities in various neurotransmitters or their receptors have now been reported in relevant brain-stem regions in infants with SIDS.\textsuperscript{97} To date, the most robust evidence for a neurochemical abnormality comes from research on the medullary 5-hydroxytryptamine system, in that approximately 50 to 75\% of infants with SIDS appear to have abnormalities in this system.\textsuperscript{34,98-100} The medullary 5-hydroxytryptamine system, which is considered critical for the modulation and integration of diverse homeostatic functions, according to the level of arousal,\textsuperscript{103} is involved in ventilation and gasping,\textsuperscript{82,83,102} thermoregulation, autonomic control,\textsuperscript{103} responses to carbon dioxide\textsuperscript{104} and oxygen,\textsuperscript{105} arousal from sleep,\textsuperscript{106} and hypoxia-induced plasticity.\textsuperscript{107} Abnormalities in 5-hydroxytryptamine neuronal number and differentiation, receptors, or transporter have been reported in the medulla of infants with SIDS, as compared with control infants, in four independent data sets.\textsuperscript{34,98-100} Given the wide array of homeostatic functions modulated by the medullary 5-hydroxytryptamine system, sudden death may result from a convergence of defects in protective responses to homeostatic stressors during sleep that are modulated by 5-hydroxytryptamine, probably in conjunction with related neurotransmitters.

**RECOMMENDATIONS FOR RISK REDUCTION AND COUNSELING**

Risk-reduction recommendations include putting infants to bed in the supine position on a firm mattress, preferably with a pacifier (mechanism unknown) and in a shared room (but in a separate bed).\textsuperscript{6,108} Prone and side sleeping, overheating, bed sharing, soft bedding, and smoking by mothers during pregnancy or around infants should be avoided.\textsuperscript{6,108} Home cardiorespiratory monitoring of apnea and bradycardia is not recommended because it has not been shown to prevent SIDS.\textsuperscript{87,109} However, efforts are under way to develop more sophisticated and sensitive measures of the putative subclinical cardiorespiratory deficits in infants who are at risk for SIDS.\textsuperscript{56,59}

Grief counseling for families that have lost an infant to SIDS is especially challenging in light of the sudden and unwitnessed nature of the infant’s death, the lack of a universally accepted biologic explanation for the death, and possible suspicion by others of foul play. However, important counseling strategies for families with infants who have died of SIDS have been devised.\textsuperscript{110} Of major concern in such families is the risk of SIDS in subsequent siblings. Although in such cases there is an increase in risk, it is minimal. For example, with an assumed incidence of 0.7 case per 1000 for the first infant and a relative risk of recurrence in a sibling of 5, it would be estimated that 99.6\% of subsequent siblings would survive infancy.\textsuperscript{25}

**CONCLUSIONS**

Current evidence suggests that SIDS involves a convergence of stressors that probably results in the asphyxia of a vulnerable infant who has defective cardiorespiratory or arousal defense systems during a critical developmental period when immature defense mechanisms are not fully integrated. Thus, our current understanding of the pathogenesis of SIDS reflects the simultaneous juxtaposition of multiple events that, when taken individually, are far less powerful than the result of their chance combination. SIDS remains a ma-
Figure 3. The Serotonergic System and Possible Effects on Homeostatic Function.
The serotonergic system is considered to be critical for the modulation and integration of diverse homeostatic functions. The medullary level of the brain stem (black line in Panel A) includes regions involved in the regulation of upper-airway control, respiration, temperature, autonomic function, and the sympathetic nervous system. In the medulla of an infant with the sudden infant death syndrome (SIDS), tissue autoradiography that was performed with the use of a specific radioligand shows a generalized reduction in binding to the 5-hydroxytryptamine type 1A receptor (Panel B), as compared with that in a control infant at the same postconceptional age (Panel C).

ARC denotes arcuate nucleus, DMX dorsal motor nucleus of the vagus nerve, GC ganglion cells, HG hypoglossal nucleus, NA noradrenaline, NTS nucleus tractus solitarius, PGCL paragigantocellularis lateralis, PreBot pre-Bötzinger complexes, and ROb raphe obscurus.
jor problem that mandates continued interdisciplinary efforts for its ultimate resolution.

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