

# Sudden Infant Death Syndrome and Sudden Unexpected Infant Death

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## Abstract

*Sudden infant death has haunted humanity since Biblical times, and many people are still confused about how to differentiate sudden infant death syndrome from other causes of sudden infant death, such as myocarditis or congenital heart disease. Because of the difficulty of diagnosis, the authors say that SIDS has become a “diagnostic dustbin,” but unnecessarily so. They provide the diagnostic criteria for SIDS, review other causes of sudden infant death that may mimic SIDS, and make several recommendations regarding ways to reduce its incidence as well as ways to improve investigations of SIDS cases. They advocate for the adoption of a universally accepted SIDS definition, as well as standardized protocols for investigation into the circumstances of death and the postmortem examination. The use of standardized protocols will improve diagnostic accuracy, which in turn impacts vital statistics, as well as resource allocation for further study. Most importantly, accurate diagnoses may help bereaved parents and other survivors who struggle to understand this painful loss.*

## Introduction

Sudden infant death has haunted humanity since Biblical times when King Solomon was called upon to determine the true mother of an infant who died in the night (I Kings 3:19). Many natural and unnatural causes, including accidental overlaying and inflicted suffocation, have been proposed to explain its occurrence (Behlmer, 1979; Byard, 1994; Byard & Hilton, 1997; Bacon, 2003). A diagnosis of sudden infant death syndrome (SIDS) is made today when an infant is found lifeless and a careful review of the medical and family history, investigation of the scene where the infant was discovered unresponsive, and a thorough postmortem examination yield no satisfactory explanations. Yet, it must be remembered that the postmortem findings after accidental or inflicted asphyxia as well as some natural diseases are often minimal (Byard, 1996; Byard & Krous, 1999; Byard & Beal, 1993). Nevertheless, the suggestions that SIDS is a “diagnostic dustbin” (Emery, 1989) or a “diagnosis in search of a disease” (Byard, 1995) reflect imprecisi-

on in diagnoses and the uncertainties that surround possible etiologies and mechanisms. So it is as true today as in decades before that accurate diagnosis remains critically dependent upon competent and thorough case investigation. In addition, as new technology becomes available, new diseases are being discovered that will explain some of these deaths (Byard, 2004).

This review focuses upon causes of sudden infant death, emphasizing SIDS; and places SIDS in perspective with other entities that may mimic it. It concludes with recommendations for the investigation of these cases.

## Sudden Death Infant Syndrome

### Definition

SIDS was defined by a National Institutes of Child Health and Human Development (NICHD) expert committee as “the sudden death of an infant less than one year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history” (Willinger, James, & Catz, 1991). Despite the appearance of more than 5000 papers in the National Library of Medicine at the National Institutes of Health, the current NICHD definition differs from the original definition only by inclusion of death scene investigation and specification of an upper age limit of one year (Beckwith, 1970). Stratification of the NICHD definition that includes a general definition for death certification and subcategories for research purposes has been recently proposed (Beckwith, 2003).

The NICHD definition for SIDS is widely accepted in the United States, but is less well accepted in other countries. Other definitions appearing in the literature conflict with that of NICHD and may differ with respect to an association with sleep, different age ranges, absence of death scene investigations, and the mandating of ancillary tests. Such deaths may be further subclassified based on the presence or absence of minor pathological findings

(Cordner, 1995; Beckwith, 1993; Sturmer, 1998; Rambaud, Guilleminault, & Campbell, 1994).

International acceptance of a definition is critical to standardization of the SIDS diagnosis. Failure to agree upon a definition will inevitably cause confusion among pathologists, scene investigators, SIDS families, and researchers. Often published research provides no specific information regarding definitions and death investigation, making its applicability to SIDS difficult, if not impossible, to ascertain. There is also a clear need to agree upon pathologic criteria for SIDS, as has been recently attempted (Rognum et al., 2004).

In the final analysis, SIDS remains a diagnosis of exclusion, and the term should not be used if the investigation is suboptimal, or there is significant but inconclusive evidence of possible accidental asphyxia, inflicted injuries or natural disease. It is worth remembering that the use of the age range during which SIDS typically occurs and the absence of significant pathologic findings can be viewed as positive criteria for a diagnosis of SIDS.

### **Epidemiology, Risk Factors, and Public Education**

SIDS rates in developed countries are generally near 0.5 deaths per 1000 live births (Hauck, 2001). Prior to national risk reduction campaigns in Western Europe, Scandinavia, Australia, New Zealand, and the United States, rates typically exceeded 2.0 per 1000 live births. From 2000 to 2001, the SIDS rate declined by an additional 11 percent in the United States (Mathews, Menacker, & MacDorman, 2003).

Risk reduction programs, like the 'Back to Sleep' campaign in the United States, have successfully educated the public to avoid placing infants prone or overwrapping them for sleep, and to avoid exposing infants to gestational and postnatal cigarette smoke. Ill-advised opinions to the contrary have been refuted and must be ignored (Goldwater, 2003). Breast feeding is also recommended, but its role in SIDS remains controversial, due in part to lack of precision in the descriptions of breastfeeding in certain studies (Alm, et al., 2002; Byard, 1998; Ford, et al., 1993; Gordon, et al., 1999; Hauck, 2001; Mitchell, Esmail, Jones, & Clements, 1996).

The majority of SIDS deaths occur when infants are between the ages of 2 and 6 months (Beckwith, 1973). More deaths occur during winter than summer months, but the predilection for deaths during

the winter months is declining (Beal, Need, & Byard, 1994; Douglas, Alexander, Allan, & Helms, 1996; Douglas, Helms, & Jolliffe, 1998; Haglund, Cnattingius, & Otterblad-Olausson, 1995; Helweg-Larsen, Bay, & Mac, 1985). High-risk infants are more often born into families with lower socioeconomic status and with less maternal education. They frequently have young mothers, are the product of pregnancies with short intergestational intervals with diminished prenatal care, and are male, of high birth order, prematurely born, and have lower birth weights (Hauck, 2001; Peterson, vanBelle & Chinn, 1982). Such infants often have documented upper respiratory infections in the days preceding death (Krous, Nadeau, Silva, & Blackbourne, 2003). Maternal use of illicit drugs, particularly of opiates, is associated with increased risk as well (Alm, et al., 1998; Bulterys, 1990; Dwyer & Ponsonby, 1995; Haglund & Cnattingius, 1990; Li & Daling, 1991; Mitchell, et al., 1993; Ponsonby, Couper & Dwyer, 1996; Schlaud, Kleemann, Poets, & Sens, 1996).

Numerous studies confirm that infants of mothers who smoke during pregnancy are at increased risk of SIDS (Hauck, 2001; Alm, et al., 1998; Mitchell & Milerad, 1999.) It has been suggested that a significant number of infants who had been placed prone for sleep may not have died of SIDS had they not also been exposed to cigarette smoke (Blair, et al., 1996; Wisborg, Kesmodel, Henriksen, Olsen, & Secher, 2000).

Ethnicity plays an important role in the risk for SIDS with Native American, indigenous populations, and African-American infants at higher risk for SIDS than white and Asian infants. Rates are lowest in Asian communities (Adams, 1985; Alessandri, Read, Burton, & Stanley, 1996; Blok, 1978; Bulterys, 1990; Hauck, et al., 2003; Kinney, et al., 2003; Lee, Chan, Davies, Lau, & Yip, 1989; Mitchell, et al., 1993; Oyen, Bulterys, Welty, & Kraus, 1990). Native Americans in Oklahoma had rates not significantly different than whites before the 'Back to Sleep' campaign (Kaplan, Bauman, & Krous, 1984). Although SIDS rates have declined nationwide since the campaign, the disparity between white and African-American infant death rates has increased (Unger, et al., 2003). SIDS rates for African-American and Native American infants were 2.2 and 2.8 times that for non-Hispanic white mothers between 2000 and 2001 (Mathews, Menacker, & MacDorman, 2003). Campaigns aimed at reducing SIDS rates in African-American communities may be most effective when advocating

avoidance of adult bedsharing, as well as sofa sleeping, shared sleeping, soft bedding, and pillows (Hauck, et al., 2003; Rasinski, Kuby, Bzdusek, Silvestri, & Weese-Mayer, 2003; Unger, et al., 2003).

Infant mortality in isolated indigenous groups is difficult to profile given that death scene evaluations and postmortem examinations may not follow standard protocols (Iyasu, Rowley, & Hanzlick, 1996; Krous & Byard, 2001). For example, infant deaths have been attributed to SIDS in isolated parts of Australia without autopsies having been performed (Byard, 2001).

In several studies, prone sleep position has been identified as one of the most important risk factors for SIDS (Dwyer, Ponsonby, Newman, & Gibbons, 1991; Hauck, 2001; Klonoff-Cohen & Edelstein, 1995; Taylor, et al., 1996). A recent population-based case-control study in California from May 1997 through April 2000 found that infants placed prone or on their sides for sleep had at least twice the risk for SIDS compared with infants placed on their backs (Li, et al., 2003). In the same study, infants were at the highest risk for SIDS when they were placed initially on their side and found prone, or when they were usually placed supine but then placed in an unaccustomed prone or side position, in which case the adjusted odds ratios were 8.2 and 6.9, respectively.

Bedsharing, especially when associated with maternal smoking, has been considered a risk factor for SIDS (Hauck, 1997; Kemp, et al., 2000; Krous, Nadeau, Byard, & Blackbourne, 2001; McGarvey, McDonnell, Chong, O'Regan, & Matthews, 2003; Unger, et al., 2003). Not all researchers agree, however (Mosko, Richard, McKenna, & Drummond, 1996). Much of this controversy ultimately results from a lack of reliable data in living controls and from inconsistency in the definition of the term 'bedsharing.' For example, bedsharing may or may not be equated with co-sleeping. In other cases, the frequency of bedsharing is not specified, and in still others associations between smoking and the safety of the sleep environment have not been clarified. Until these issues are addressed, the real risk of bedsharing will not be known.

A study describing four infants dying within 24 hours of receiving diphtheria-tetanus-pertussis vaccine suggested that SIDS is caused by immunization (Morbidity and Mortality Weekly Report, 1979). Subsequent reports from North America, Europe and Australia demonstrated that SIDS is less common in infants who have been immunized (Beal, 1990; Bernier, Frank, Dondero, & Turner, 1982; Cherry,

Brunell, Golden, & Karzon, 1988; Fleming, et al., 1997; Mortimer, 1987; Walker, Jick, Perera, Thompson, & Knauss, 1987). Decreasing the age of first immunization in South Australia from three to two months was not accompanied by a fall in the median or mean age of SIDS infants, as would be expected if the two events were causally related, and less than half of infants dying of SIDS in that community had actually been immunized (Beal, 1990; Byard, MacKenzie & Beal, 1997).

Twins were identified in several studies to be at higher risk for SIDS (Dalveit, Vollset, Otterblad-Olausson, & Irgens, 1997; Ramos, Hernandez, & Villanueva, 1997). However, not all investigators have confirmed this (Ramos, et al., 1997). In one recent study, the higher crude relative risk of SIDS in twins compared to singletons resulted from a higher proportion of twins having low birth weights (Platt & Pharoah, 2003). Same sex twins do not appear to be at higher risk for SIDS, suggesting that zygosity is not a significant factor in the etiology of SIDS (Peterson, Chinn & Fisher, 1980).

### Pathology and Pathogenesis

At postmortem examination, the body of a typical SIDS infant appears well developed, hydrated, and nourished. However, body weights are generally below the 50th percentile expected for age (Beckwith, 1973; Siebert & Haas, 1994). If the infant is found clothed, the diaper is typically wet, and correspondingly, the bladder is empty. The lungs are congested, but pneumonia is not evident to the naked eye. The thymus is of normal size and does not reveal significant involutinal changes consistent with the generally good clinical health of the infant before death. Similarly, the adrenal glands do not reveal lipid depletion.

Although SIDS likely represents more than one disease, its unique age distribution, association with sleep, and the usual presence of intrathoracic petechiae suggest a final common pathway to death. The vast majority of SIDS deaths occur between 30 and 180 days, and intrathoracic petechiae are identified in more than 80% of cases (Beckwith, 1973; Krous, 1984; Krous & Jordan, 1984). Their distribution raises the possibility that the terminal mechanism in SIDS is unsuccessful breathing against an obstructed upper airway, and perhaps obstruction more likely in the pharynx, rather than due to oronasal compression from lying face down on a sleeping surface (Beckwith, 1970; 1988; Krous, 1984; Krous & Jordan, 1984; Krous, Nadeau, Silva, & Blackbourne, 2001a).

A triple risk hypothesis that links the state of an infant's development, environmental risk factors, and the pathological findings in SIDS has been proposed (Filiano & Kinney, 1994). When factors from these three variables intersect, the infant can die catastrophically and present as SIDS. Sophisticated analyses have detected defects in chemoreceptors of the arcuate nucleus and abnormalities in the medullary serotonergic network that appear to adversely affect the central control of respiration, particularly during sleep (Kinney, et al., 1995; Kinney & Filiano, 2001; Panigraphy, et al., 1997; 2000). Abnormalities in receptor binding to the neurotransmitter serotonin (5-HT) in medullary regions containing 5-HT neurons that are critical for the regulation of cardiac function and respiration, as well as central chemosensitivity during sleep, have been identified recently in SIDS cases compared with postmortem controls (Kinney, et al., 2003). Since these changes were identified among Native American infants in the Northern Plains, whose parents have high rates of smoking and alcoholism, and whose SIDS rate is almost 6 times higher than in U.S. white infants, it was hypothesized that prenatal exposure to cigarette smoke and/or alcohol may contribute to abnormal fetal medullary 5-HT development in infants at increased risk of SIDS (Bulterys, 1990).

Other neuropathologic changes have been identified in SIDS infants as well, including upper and lower airway peripheral chemoreceptor and baroreceptor abnormalities (Cutz & Jackson, 2001; Cutz, Ma, Perrin, Moore, & Becker, 1997; Gillan, Curran, O'Reilly, Cahalane, & Unwin, 1989; Lack, Perez-Atayde & Young, 1986; Perrin, Cutz, Becker, & Bryan, 1984; Perrin, McDonald, & Cutz, 1991; Ramos, Matturri, Biondo, Ottaviani, & Rossi, 1998). Increased numbers of neuronal dendritic spines and brainstem gliosis (the former thought to represent a delay in neuronal maturation while the latter has been proposed as a marker for previous hypoxic damage), have also been identified in certain infants who die of SIDS (Becker & Takashima, 1985; Becker, 1990).

Given that recurrent hypoxemia has been proposed as an important pathophysiological event underlying SIDS deaths, vascular endothelial growth factor (VEGF), a protein that is produced in response to changes in oxygenation even within the physiologic range, was measured in the cerebrospinal fluid (CSF) of 51 SIDS infants and in 33 control infants whose cause of death was deter-

mined. Elevated mean CSF VEGF levels (308.2 +/- 299.1 pg/dL) in SIDS cases compared to mean levels in the control group (85.1 +/- 82.9 pg/dL) suggested that hypoxia may be a frequent event preceding death in some infants (Jones, et al., 2003).

The hypothesis that SIDS is linked to hyperperfusion of the brain stem secondary to vertebral artery compression from head rotation or extension during prone sleep has been evaluated in living infants and in postmortem specimens (Deeg, et al., 2001; Deeg, Alderath, & Bettendorf, 1998; Gilles, Bina, & Sotrel, 1979; Pamphlett & Murray, 1996; Pamphlett, Raisanen, & Kum-Jew, 1999). Recent work, however, is not supportive of this concept (Krous, Nadeau, Silva, & Blackburne, 2001b; Vanhatalo, Nikolajev, Kiekara, Seuri, & Riikonen, 2003).

Obstructive apnea associated with pharyngeal collapse during rapid eye movement sleep and abnormal narrowing of upper airways related to posterior positioning of the mandible, narrowing of the oropharynx and enlargement of the tongue has been implicated as a factor in SIDS deaths (Engelberts, 1995; Guilleminault, et al., 1979; Kahn, et al., 1988; Siebert & Haas, 1991; Thach, Davies & Koenig, 1988; Tonkin, Stewart, & Withey, 1980). Other investigators have found alveolar surfactant abnormalities, suggesting that certain infants are at higher risk of alveolar collapse, but confirmatory data are again lacking (Talbert & Southall, 1985). Similarly, the evidence is inconsistent regarding a significant role for laryngospasm and gastroesophageal reflux in SIDS (Ariagno, Guilleminault, Baldwin, & Owen-Boeddiker, 1982; Jolley, 1992), although there has been a recent plea to reconsider the latter association (Thach, 2000). Cardiac dysfunction reflected as either an increase in cardiac rate or as disturbances in rhythm, especially long QT interval, have been identified in infants who subsequently died of SIDS (Ackerman, et al., 2001; Schwartz, et al., 1998; Southall, et al., 1988). Given the limitations that are often present in the size of the study populations, the overall incidence and nature of underlying cardiac problems in SIDS infants remains a subject of ongoing debate. A study of 93 consecutive cases of sudden unexpected infant death in Arkansas, in which fresh cardiac tissue was submitted for molecular analysis, identified two cases, both of whom were bedsharing, with sodium channel mutations associated with prolonged QT interval. None of the 400 control cases had this finding (Ackerman, et al., 2001).

The winter peak of deaths and the frequent association of SIDS with upper respiratory illnesses make an infectious etiology attractive (Blackwell, Weir, & Busuttill, 2001). However no single agent has been consistently found (Carmichael, Goldwater, & Byard, 1996; Krous, Nadeau, Silva, & Blackbourne, 2003). Synergy between a variety of microorganisms, some of which produce toxins, has been proposed to link SIDS to infections (Opdal, Vege, Stave, & Rognum, 1999; Vege & Rognum, 1999; Vege, Rognum, & Anestad, 1999; Vege, Rognum, Aasen, & Saugstad, 1998). *Clostridium botulinum*, *Escherichia coli* and cytomegalovirus are organisms most commonly implicated. However, other studies have either failed to reveal these organisms in SIDS cases, or have found equal or greater numbers of positive control cases (Byard, Moore, Bourne, Lawrence, & Goldwater, 1992; Smith, Telfer, & Byard, 1992). In a recent study, upper respiratory infections (URIs) within 48 hours of death, respiratory inflammation, and postmortem culture results were compared in 155 infants dying of sudden infant death syndrome and 33 control infants who died of accidents or inflicted injuries (Krous, Nadeau, Silva, & Blackbourne, 2003). URIs were present in 39% of SIDS cases and in 40% of control cases. Bronchial, bronchiolar, and pulmonary interstitial lymphocytic infiltration was similar between groups, and cultures were positive in 80% of SIDS cases, 78% of which were polymicrobial, while among control cases, 89% were positive, with 94% being polymicrobial. Another study used reverse transcriptase polymerase chain reaction techniques for the detection of influenza A+B virus in 118 cases of natural and non-natural infant deaths, some of whom had interstitial pneumonitis (IP). This study revealed only influenza B virus genome in five, but neither parainfluenza virus 3 nor respiratory syncytial virus were present (Bajanowski, Rolf, Jorch, & Brinkmann, 2003). Previous studies from this group have also detected adenoviruses and cytomegaloviruses (Bajanowski, et al., 1996; Cecchi, Bajanowski, Kahl, & Wiegand, 1995). In summary, the role of respiratory infection and inflammation in SIDS remains controversial, but it is an important area for continued investigation.

Pulmonary siderophages are occasionally identified, but their presence should not be interpreted as unequivocal evidence of previous attempts at suffocation (Becroft & Lockett, 1997; Byard, Stewart, Telfer, & Beal, 1997). Despite earlier claims (Shatz, Hiss, & Arensburg, 1991; 1997; Shatz, Hiss, Hammel, Arensburg, & Variend, 1994), thickening of the laryngeal basement membrane is not a

reliable marker for SIDS (Krous, et al., 1999; van Landeghem, Brickmann, & Bajanowski, 1999).

## Other Causes of Sudden Infant Death

### Accidental suffocation

Accidental suffocation typically occurs in unsafe sleeping environments, including poorly constructed cribs and/or chaotic bedsharing. Crib construction must now meet federal safety guidelines. Unfortunately, unsafe cribs are still used with tragic consequences by some who lack the financial resources to purchase newer or safer cribs. Infants may suffocate from their head passing between widely placed crib slats, or becoming wedged between a crib and a wall wherein the infant's nose and mouth are obstructed. Bedsharing is most dangerous when an infant is placed between parents on a soft mattress and is covered by blankets or a quilt/duvet (Beal, Baghurst, & Antoniou, 2000; Beal, et al., 1995; Beal & Byard, 2000). Large parents, especially when intoxicated, sedated or fatigued, increase the risk of overlaying deaths (Byard, 1994; Byard & Hilton, 1997). Certain infants are also prone to rapid respiratory arrest if there is even a short period of airway occlusion. Such deaths have been documented during breast feeding. The autopsy findings in such cases are identical to those found in SIDS deaths (Byard & Burnell, 1995; Mitchell, Krous, & Byard, in press). Until at-risk situations and vulnerable infants can be more precisely identified, placing an infant in a crib beside but separate from the parental bed is recommended.

### Infanticide

Occult infanticide has been estimated to account for 1.3% (McClain, Sacks, Froehlke, & Ewigman, 1993) to 10% (Emery, 1985) of cases labeled as SIDS. Although the true percentage is unknown, the lower figure is probably more accurate. Multiple murders of infants originally attributed to SIDS in the same family continue to capture the interest of the media (Firstman & Talan, 2001). Inflicted injuries causing infant death can take many forms. Fortunately, in most of these cases the cause and manner of death is obvious. On the other hand, one of the most difficult and important challenges facing forensic and pediatric pathologists, pediatric pulmonologists, sleep physiologists, child abuse experts, and the legal community, is distinguishing SIDS from suffocation, particularly when soft surfaces, such as pillows, are used. Short of actual observation, this distinction can be extremely difficult, if not impossible.

Two infants with apnea and cyanosis who were reported as "near-miss" SIDS were subsequently documented to be victims of attempted suffocation by their mothers (Berger, 1979). It is now apparent they were examples of the phenomenon known as Munchausen's syndrome-by-proxy (MSBP), which has been described subsequently in other reports (Meadow, 1977; 1982). MSBP may be characterized by recurrent apnea, cyanosis, seizures, a history of repeated resuscitation and sudden death. A history of sudden death among infant and early childhood siblings is not uncommon. The usual perpetrator is the mother, approximately three-fourths of whom have suffered emotional, physical or sexual abuse when they were young. An important clue to the diagnosis of MSBP is that the reported nonfatal life-threatening episodes occur only in the presence of the same caretaker, who is usually the mother. Covert video surveillance has documented examples of MSBP (Samuels, McClaughlin, Jacobson, Poets, & Southall, 1992; Southall, Plunkett, Banks, Falkov, & Samuels, 1997), and should be considered if MSBP is suspected. It may not only provide necessary medicolegal evidence, but also enable rescue of an infant from either serious injury or death.

A longitudinal perspective on this problem is provided by a recent California study covering an 18-year period that showed no absolute increase in inflicted infant deaths. However, the study showed that proportionately more deaths were the result of infanticide due simply to the marked reduction in numbers of SIDS deaths (Krous, Nadeau, Silva, & Byard, 2002). Similar findings have been reported elsewhere (Mitchell, Krous, Donald, & Byard, 2000).

Misdiagnosis of fatal inflicted injuries is unquestionably a consequence of inadequate case investigation. For example, it appears that variable standards were applied to investigations and autopsy procedures in the report of 42 cases of infant homicide misdiagnosed as SIDS (Meadow, 1999). Scanty and inexpert investigations, including failure to record significant findings regarding the pathology and circumstances of sudden infant death, have been documented during audits (Bacon, 1997). This clearly demonstrates the need for higher standards and confirms the axiom that "bad pathology produces bad diagnoses" (Byard & Krous, 1999). Failure to competently investigate these cases may jeopardize police investigations, allow perpetrators to go undetected, and place siblings of the dead infant at risk of injury or death. On the other hand, in cases where the infant died of an unidentified rare disorder, parents

may be unjustly accused and left unable to refute possible allegations of poor infant care.

Multiple infant deaths in one family should prompt consideration not only of homicide but also of rare inherited metabolic or cardiac diseases. The dictum that the first death is SIDS, the second death is "undetermined" and the third death is automatically "homicide" cannot be supported, as inflicted trauma is only one possibility.

### Metabolic Diseases

Metabolic disorders, especially those characterized by defective fatty acid oxidation, have been documented in cases of sudden infant and early childhood death (Bennett, et al., 1991; Bennett & Powell, 1994; Byard, 2004). A number of studies suggest that these disorders comprise a small percentage of cases misdiagnosed as SIDS (Arens, et al., 1993). Fatty acid oxidation defect disorders are characterized clinically by a history of hypoketotic hypoglycemia and lethargy, especially after fasting, acute life threatening events (ALTEs), coma and sudden death. A history of sudden death in childhood siblings is not uncommon, and hepatic steatosis is seen at postmortem examination (Brackett, et al., 1994; Wang, Fernhoff, Hannon, & Khoury, 1999). Medium chain acyl CoA dehydrogenase (MCAD) deficiency is the most common of these diseases. Tandem mass spectrometry generally allows easy and accurate diagnosis (Bennett & Rinaldo, 2001; Chace, Hillman, Van Hove, & Naylor, 1997; Chace, et al., 2001).

### Congenital Cardiac Anomalies

Obstructive left heart malformations, anomalous coronary arteries, and endocardial fibroelastosis are conditions associated with sudden death in infants (Thornback & Fowler, 1975; Valdes-Dapena & Gilbert-Barness, 2002; Vetter, 1985). Sudden infant death has also been associated with anomalous pulmonary venous connections (Byard & Moore, 1991). Ventricular septal defects are occasionally seen, but are not necessarily the cause of death, especially if they are small, or if right ventricular hypertrophy and hypertensive pulmonary arteriopathy are absent. The vast majority of congenital heart defects are recognized clinically, and today most have undergone some sort of corrective surgery, even if palliative. Given the rarity of such conditions that come to the jurisdiction of the medical examiner, consultation with pediatric pathologists can be helpful in their clinical and anatomic interpretation.

## Infections

Myocarditis is an important infectious cause of sudden death in infants (de Sa, 1986; Lau, 1994; Norman, Taylor, & Clarke, 1990; Rasten-Almqvist, Eksborg, & Rajs, 2002; Sharief, Khan, & Conlan, 1993). Since myocarditis is often not apparent to the naked eye, examination of numerous microscopic sections, including the conduction system, is advisable (Rasten-Almqvist, et al., 2002). Coxsackie virus is the most common organism causing myocarditis, and can be identified by either culture or PCR techniques (Baasner, Dettmeyer, Graebe, Rissland, & Madea, 2003; Lau, 1994). Mumps virus has also been identified in cases of myocarditis causing sudden infant death (Brown & Richmond, 1980). Other viral agents associated with myocarditis include adenovirus and cytomegalovirus (Lozinski, et al., 1994, Shimizu, et al., 1995; Sun & Smith, 1984). In the absence of myocardial degeneration and necrosis, mild focal lymphocytic infiltration should not be considered lethal (Rognum, et al., 2004). Sepsis, pneumonia, and meningitis caused by a variety of bacterial organisms also account for sudden deaths of infants. The most common organisms responsible for these entities are streptococcus, staphylococcus, *Neisseria meningitidis*, and *Escherichia coli*.

## Conclusions and Recommendations

Even though overall death rates have declined since the introduction of campaigns publicizing risk factors, SIDS remains one of the most common causes of postneonatal death in developed countries. For SIDS rates to decline further, public health activities must reach communities that have remained difficult to engage in public health initiatives due to unstable housing, low socioeconomic status, limited educational background, and cultural and language barriers (Willinger, et al., 1998; Willinger, Ko, Hoffman, Kessler, & Corwin; 2000).

It is unfortunate that the media often publicizes new "causes" of SIDS that have not been subjected to peer-review and publication in medical journals, or that have originated from specific-issue groups that use the fear of SIDS to advance their objectives. For example, some special interest groups claim to this day that immunizations cause SIDS, a claim that must be rebutted by recognized experts. Essentially all reliable literature documents that immunization is associated with a reduced risk of SIDS, and that immunizations should be administered according to recommended schedules to pro-

vide protection against numerous childhood illnesses, some of which are fatal or able to cause permanent disability. In the absence of accurate public education about SIDS, parents may ignore warnings about proven risk factors, such as prone sleeping position and tobacco smoke exposure.

Efforts to improve the evaluation of cases of sudden infant death must be redoubled, with the goal of adopting a universal SIDS definition using standardized protocols for investigation of both the circumstances of death and post-mortem examination. Any new definition of SIDS should aim for worldwide endorsement by professional societies. The use of standardized protocols will maximize the opportunity for accurate diagnoses that are so important for death certification and vital statistics. Accurate diagnoses are also crucial to funding agencies in the process of resource allocation. Most importantly, bereaved parents and other survivors also benefit from accurate diagnoses. Future pregnancy counseling is critically dependent upon accurate diagnoses in cases of sudden infant death.

Finally, research into sudden infant deaths must continue. Even though the number of cases has declined, SIDS has not disappeared. Epidemiologic research has produced spectacular results in terms of reducing death rates. However, the research provides only clues to underlying mechanisms. Investigation of post-mortem specimens is critical in the development of these answers. In order to compare findings among research groups, especially those who rely upon post-mortem specimens, investigators must specify the definition of SIDS that was used. It is therefore counterproductive to use inherently contradictory diagnostic terminology such as "sudden infant death syndrome with myocarditis" (Rambaud, et al., 1994) or "cardiovascular causes of SIDS" such as myocarditis, rhabdomyomas and congenital heart disease (Valdes-Dapena & Gilbert-Barness, 2002). Research also benefits by noting the study interval during which time the cases were collected, whether standard protocols were followed, and whether location of death was actually investigated. It may even be helpful to identify the types of centers where the autopsies were conducted. In order for SIDS to avoid becoming a 'diagnostic dustbin' (Emery, 1989), practitioners and researchers alike must pursue the investigation and diagnosis of unexpected infant deaths with increased rigor. The entire community will benefit from such an approach.

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