Comment on Systemic Issues being examined by the Inquiry into Pediatric Forensic Pathology in Ontario

Dr. Ernest Cutz

I have reviewed the "List of Systemic Issues" currently available on the website of the Inquiry into Pediatric Forensic Pathology in Ontario (the "Inquiry").[1] The following document reflects my own personal views and comments on select questions posed in that list. My comments reflect over 35 years of experience in Pediatric Pathology, including pediatric forensic pathology.

I. Institutional Considerations

5. *Should Ontario have an institutional setting dedicated to pediatric forensic pathology, or should pediatric services be delivered within a forensic pathology institutional setting?*

In essence, it is my view that the pediatric pathology work performed in Ontario should not be all be performed by the same institution. Rather, pediatric autopsy work should be divided between HSC an OCCO. I say this for the following reasons:

a) Approximately 90 per cent of pediatric cases investigated under the Coroner's Warrant result from death due to natural causes or pediatric disease. These cases are thus not "forensic" by nature. It is appropriate that pediatric pathologists from the Hospital for Sick Children ("HSC") perform the autopsies in these cases. It is my view, however, that HSC should only perform autopsies on these "medical/natural death cases". Therefore, there would no longer be a need for a Pediatric Forensic Pathology Unit ("OPFPU") at HSC (see PFP 117927/1-5;Vol.2 tab 2). Furthermore, it is my view that there is an incompatibility between the principal mission of HSC as being dedicated to academic pursuits and research and OCCO, which excludes research (see PFP 03373/14;Vol 2 tab 57; in effect since Feb. 2007). I believe that the institutional link between HSC and OCCO should be discontinued.

[1] See http://www.goudgeinquiry.ca/systemic_issues/pdf/List_of_Systemic_Issues.pdf (available at the time of writing)

b) In summary, it is my view that the Division of Pathology at HSC, and other Pediatric Pathology services at other large academic centers, are best suited to provide high quality pediatric pathology services focusing on academic aspects that include the diagnosis and investigation of pediatric diseases.

c) However, to ensure that infants and children are protected from harm and abuse, the remaining ten per cent of cases that include clear homicides or criminally suspicious deaths are best handled by qualified forensic pathologists whose training and experience lies primarily in the examination of violent death, homicides and such. The best setting to perform these autopsies (which total approximately 10-15 cases per year) is at OCCO, which has the qualified staff and required facilities to conduct the necessary investigations.

d) In terms of the pediatric disease cases, the best protection against wrongful accusations in pediatric cases is the provision of a correct diagnosis of natural disease based on a solid scientific foundation. The diagnosis of pediatric disease in the 21st century is based on sophisticated methods of cellular and molecular biology (i.e. testing for genetic or metabolic disorders). This testing requires special expertise and facilities, all of which are available at HSC, but are not available at OCCO.

e) Since research and education into pediatric disease is outside the mandate of OCCO, the responsibility and the provision of resources for this essentially patient-related activity should be assumed by the Ministry of Health and Long term Care ("MHLTC").

10. *What is the most cost efficient way of delivering quality pediatric forensic pathology services? For example, what are the advantages and disadvantages of using staff doctors or fee-for-service doctors?*

a) Staff Pathologists based at leading Pediatric Academic Institutions, such as HSC, can deliver the most cost-efficient and highest quality pediatric pathology services. All staff are qualified and experienced Pediatric Pathologists who are also cross-appointed to the University of Toronto and thus participate fully in research and educational activities.

b) The combination of high-level diagnostic skills in diagnosing pediatric disease, research into disease pathogenesis, and education ensures that the work of these pathologists is high quality and also serves to educate the next generation of pediatric pathologists, thereby addressing the shortage of professionals in this specialty.

II. The Post Mortem Examination

13. *What is the approach that best balances the objective that no individual be wrongly accused of child abuse with the objective that children be protected from abuse? What are the relative merits of "thinking dirty" or "thinking truth" or other alternatives?*

14. *How is scientific objectivity best maintained throughout the examination to avoid "tunnel vision" that merely seeks support for an* a priori *conclusion?*

a) The objectives of questions 13 and 14 can be achieved by the provision of correct pathologic diagnoses based on solid scientific foundations. The acquisition of and advances in medical knowledge are dependent on robust scientific research that constantly evolves and progresses over time. The Inquiry has seen how this evolution in thinking occurs through exposure to the debate and recent changes in attitude with respect to the interpretation of findings relating to Shaken Baby Syndrome ("SBS"). Similar changes in attitude and thinking have occurred in the areas of Sudden Unexpected Infant Death ("SUD"), Sudden Infant Death Syndrome ("SIDS"), and related conditions. For example, during the 1990s a prevalent, early view was that SUD and SIDS occurred due to "positional asphyxia", overlaying caused by co-sleeping, or homicide. These views have not been substantiated by solid scientific evidence. Now, the prone sleeping position and co-sleeping are recognized as risk factors but are not the actual cause of death in SIDS.

b) Today we know that SIDS is a pediatric disease recognized by the World Health Organization as a distinct pediatric medical disease entity. In addition, SIDS is not a uniform entity but rather a heterogeneous multifactorial disorder with variable triggering and potentiating factors. This is as exemplified by the so-called "triple risk model", i.e. SIDS

occurs as a result of interactions involving (1) a vulnerable infant who possesses some underlining biological abnormality; (2) a critical period of development; and (3) an exogenous stressor such as maternal smoking, mild infection or an unsafe sleeping position.[2] Current thinking in this area, which reflects recent advances in molecular medicine, indicates that an underlining biological abnormality in large proportion of SUDs and SIDS cases may, in fact, be due to genetic or molecular disorders (i.e. defects in cardiac or neuronal ion channels, etc) that are now detectable by modern techniques of molecular pathology.[3]

c) Notwithstanding these changes, confusion between what are risk factors for SIDS and what is the actual cause of death in SIDS persists in certain forensic circles. Individuals in these circles continue to identify the cause of death in SIDS cases as being, for example, co-sleeping, which is inaccurate and misleading. If SIDS was due to this simple explanation, how could one explain the fact that babies have slept in these situations for many years, but only some die while many do not?

d) Identifying a baby's sleep environment as the sole factor responsible for the infant's death gives only part of the explanation and leads to feelings of guilt and, potentially, to wrongful accusations of parents and caregivers.

e) Given the importance of accurately identifying and describing cause of death, it is problematic that there is currently very limited or non-existent scientific research on SUD and SIDS. This is partly due to the fact that the mandate of OCCO, which oversees all pediatric forensic cases, does not include research into medical diseases and because the current legislation and all agreements between OCCO and HSC (including the most recent OPFU agreement, for details see PFP 03373/14, signed Feb.2007) explicitly forbid the use of tissues for medical research. Furthermore, it is my view that research scientists are discouraged from pursuing basic research into SIDS since it remains under a cloud of suspicion and subject of criminal investigation.

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[2] See Cutz Arch Pediatr Adolesc Med 157,p 292-293,2003
[3] See Hunt CE and Hauck. Can Med J 20006;174:1861-1869

f) To overcome the obstacles surrounding the use of tissues for research individual parental consent can be obtained or a legislative change, similar to that of the State of California, which authorizes and mandates research into SUD and SIDS could be made.[4] Consequently an "Ontario Center for the study of SIDS/SUDS", based on the San Diego SIDS/SUDC Research Project database model, should be established at HSC with collaboration projects that include other Ontario pediatric academic centers that perform autopsies on SIDS/SUD cases. Funding for the Center should be provided by MHLTC.

g) Further, to encourage research in SUD and SIDS, targeted, competitive, peer-reviewed research grants into SUD and SIDS in a form of "Request for Application" ("RFA") should be issued by the Government of Ontario and by the Federal Government through Canadian Institute of Health Research ("CIHR")/Institute of Child Health. The resulting research is important because it would define protocols and methods for molecular diagnoses of disorders underlying SUD and SIDS (for example, the specific channelopaties affecting the cardiovascular or nervous systems). These new diagnostic tests could provide objective scientific evidence that would be exculpatory in contentious cases of infant death. The tests would be analogous to DNA tests used currently in the criminal justice system.

III. Post Mortem Report

34. When, if at all, should the terms "SIDS" and "SUDS" be used in a post mortem report?

a) These terms are well established and widely accepted in Pediatric clinical and pathology practice. There is no compelling reason to not to use them in a post-mortem report.

b) The definition and terminology related to SIDS and SUDs has been the subject of a recent review and update by an international panel of experts comprised of paediatric and forensic pathologists with extensive

[4] See Krous HF et al Pediatrics 2004;114:492-494

experience in SIDS. The panel also included pediatricians and an epidemiologist.[5] It is important to use the correct terminology with respect to SUD and SIDS so that accurate statistics are generated to monitor the incidence and trends of SUD and SIDS as well as to ensure that well-defined groups of cases are used in research studies. My recommendation is to adopt the use the criteria and definitions outlined in the above publication in Ontario.[6]

c) With advances in SIDS research it will be possible in the future to render specific pathological diagnoses which will have the effect of removing ambiguity as to the cause and manner of death. This will reduce the number of cases that today are designated as "undetermined" or "unascertained".

IV. Role of the family

70. *Should there be guidelines for communications between the pathologist or the coroner and the family? How should an ongoing criminal or child protection investigation affect the communication?*

71. *How, if at all, can the family's need to grieve be reconciled with the work of the pathologist in a pediatric forensic death?*

a) The death of a child has a profound effect on the family unit with lifelong consequences. At present, all such deaths become the subject of police investigation and the home where the child has died becomes a "crime scene" adding further shock to the already distraught family. There is no specific counseling, education or long term follow- up. In fact, many families feel isolated and become crime suspects in the eyes of the public even though no crime has been committed.

b) Clearly a more balanced approach is needed that rests more on the presumption of innocence than implying guilt up front. One possible solution could be the involvement of a Public Health nurse or other health care professionals who are knowledgeable in infant care practices. These individuals should have initial contact with the families and should be responsible for public education, emotional support and long-

[5] For specific guidelines see Krous HF at al Pediatrics 2004;114:234-238
[6] *Ibid*

term follow-up with affected families. Further, these individuals could be trained as death scene investigators in child deaths to identify potential risk factors and to insure best infant care practices. This approach could help create a more compassionate and sensitive mechanism for investigating children's deaths.

c) In the past, pediatric pathologists sometimes interacted with SIDS and SUD families prior to and/or following the autopsy. The pathologist would explain his of her findings and help the family to cope with their grief. Some HSC staff pathologists have also interacted with SIDS parents organizations by providing information and lecturing on SIDS. My suggestion is to encourage and re-establish these links since pediatric pathologists are best qualified to explain autopsy findings in these cases. Interaction with families will have a positive effect in terms of regaining the trust of the public and also increase the profile of pediatric pathologists, helping with recruitment issue.

Finally, I support Beckwith's comments about the wisdom of pathologists refining the definition of SIDS. Other medical specialists bring important perspective to the general problem, but it is the pathologist who makes the diagnosis in individual cases.

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An International Perspective

Beckwith's observations are welcome. I am dismayed at the level of confusion about the definition of SIDS, which was highlighted at the 7th SIDS International Conference in Florence, Italy, in 2002. The unfortunate consequences of various well-intentioned proposals on definitions and diagnoses produce an increasing variability of international diagnostic practices and eliminate the possibility of meaningful intercountry comparisons. The effect has been an increasing reluctance of pathologists and coroners in many countries to apply the diagnosis of SIDS. The term *unascertained* is booming, accounting for very low rates of SIDS being reported in some countries. This has also led to an escalation of parental blame, which Beckwith has tried hard to soften.

The addition of a death scene investigation to the definition is a prime example of the caution required before changes are made. At the time the idea, aimed at providing useful additional information about infant deaths, seemed to be a good one. In retrospect, it was not. This requirement was added without proper research to identify and justify which death scene circumstances could be considered reasonably certain causes of death and which should leave the diagnosis of SIDS (or alternatives) unchanged. More than anecdotal evidence of scientific benefit should have been required. Also, greater consideration should have been given to the practical problem of inadequate resources for death scene investigation in most communities and the adverse effects on parents because of the uncertainties introduced. The current outcome is that in a few centers these investigations are being carried out by skilled personnel, the parents are treated sympathetically, and the results are interpreted with caution in relation to the cause of death. Elsewhere, however, death scene investigations are not carried out at all, and in their absence there is a reluctance to make a diagnosis of SIDS. There is also a lack of resources. Staff have difficulty gaining sufficient experience now that the incidence of SIDS has fallen. Too often the changed definition has led to the expectation that the death scene investigation should reveal a cause of death and that the parents are suspect until proved otherwise.

There are other problems attending the reluctance to use the term SIDS when the chosen alternatives (eg, *unascertained*) still fall within the original definition of a syndrome of unexplained sudden infant death. Risk factors are being promoted as causes of death (prone sleeping, for example). There are problems in the uncritical acceptance of non–evidence-based diagnostic labels as causes of death that do not meet the criteria of the *International Classification of Diseases, Ninth Revision*.[1] For example, I admire the technical aspects of the work of Kinney et al[2] on the brainstem in SIDS. However, because there cannot be true controls, the line between normality and abnormality can only be arbitrary. It is premature at this stage of knowledge to provide diagnoses such as "arcuate nucleus hypoplasia" as a cause of death.

The original SIDS concept was an enormous step forward. Changes in definition must be based on research, and pediatric pathologists should take the lead in doing so.

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1. World Health Organization. *International Classification of Diseases, Ninth Revision (ICD-9)*. Geneva, Switzerland: World Health Organization; 1977.
2. Kinney HC, McHugh T, Miller K, Belliveau RA, Assmann SF. Subtle developmental abnormalities in the inferior olive: an indicator of prenatal brainstem injury in the sudden infant death syndrome. *J Neuropathol Exp Neurol*. 2002;61:427-441.

New Challenges for SIDS Research

The preeminent pediatric pathologist and the first to coin this term, J. Bruce Beckwith, MD, reviews the historical background and evolution of attitudes toward the diagnosis of SIDS. Unfortunately, in 2003, the question of etiology and pathogenesis of SIDS is far from resolved; many questions and issues remain unanswered. Although a substantial reduction in SIDS deaths after the back-to-sleep campaign has been reported, there is still a significant number of infants who die suddenly and unexpectedly (including classical SIDS). Clearly the problem of SIDS has not gone away, and further painstaking research will be required to one day eliminate this tragedy.

In my view, the continuing problem with the definition of SIDS reflects the lack of consensus on basic issues. First, there is still no general agreement on whether SIDS by definition should be considered a disease entity or also include the deaths of previously healthy infants. Clearly, the accidental (ie, overlying)/intentional suffocation theory for SIDS should not be applied to the whole SIDS group because such cases represent only a small minority. In fact, one of the intended goals of the revised 1989 SIDS definition was to exclude such cases by thorough death scene and forensic investigation.

Second, it is evident that SIDS is not a uniform entity but rather a heterogeneous multifactorial disorder with variable triggering and potentiating factors, as exemplified by the so-called triple-risk model: (1) a vulnerable infant who possess some underlying abnormality; (2) a critical period in development; and (3) an exogenous stressor such as maternal smoking or a mild infection. In the past, many theories and hypotheses, even the most

plausible ones, have been dismissed or ignored because not all SIDS cases fit into 1 single category.

The third issue that continues to frustrate SIDS researchers is the scarcity of suitable controls; deaths of healthy infants of comparable age are exceedingly rare. Therefore, the definition of suitable controls for SIDS studies may be equally important.

I strongly support Beckwith's suggestion to organize a meeting of pathologists with experience in SIDS to address the various issues raised in his article. Hopefully a solution will be found so that SIDS research can benefit from the unprecedented recent advances in modern cellular and molecular biology. Examples include the discovery of defects in cardiac potassium (K^+) channels, mitochondrial DNA, and enzymopathies associated with sudden infant death. I believe that a full understanding of the pathobiological characteristics of SIDS is a prerequisite for rational prevention and/or treatment of this devastating pediatric disorder.

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Sudden Infant Death Syndrome: Need for Simple Definition but Detailed Diagnostic Criteria

Since the term SIDS was first used 33 years ago, the definition of this syndrome has caused lots of controversy, some tragedies, and many blessings. Without the focus on SIDS as an entity, the epidemic of infants dying in the prone sleeping position would probably have been prolonged. That the back-to-sleep campaign has saved many thousands of infants' lives is quantitatively much more important than the sad fact that the syndrome has been used to conceal homicide. The term *per exclusion* is of course a great problem constituting a persistent temptation to use it as a diagnostic dustbin.

Diagnostic work may be very complicated. The pathologist's dream would be a red lamp on the microscope lighting up when the right diagnosis is established. Very often, however, diagnoses are built on a set of observations: some positive and some negative. In the case of SIDS, most of these characteristics are negative. Until now, except for the age span, other criteria have been those of exclusion.

The current proposal by the very father of SIDS, J. Bruce Beckwith, MD, seems to be a modest attempt to define the exclusion criteria more distinctly. Besides narrowing the age span, more weight is placed on describing the circumstances and pathologic findings; for example, no similar deaths in siblings, no evidence of significant trauma, and no evidence of unexplained stress to the thymus.

Beckwith's proposal is somewhat similar to the Stavanger definition[1] we suggested in 1995 (ie, sudden death in infancy unexplained after a review of the clinical history, examination of the circumstances of death, and postmortem examination). Perhaps the Stavanger definition could be used as the generic definition encompassing the 3 categories of SIDS suggested by Beckwith.

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1. Rognum TO, Willinger M. The story of the "Stavanger-definition." In: Rognum TO, ed. *Sudden Infant Death Syndrome: New Trends in the Nineties*. Oslo, Norway: Scandinavian University Press; 1995:17-20.

SIDS: Permissive or Privileged "Diagnosis"?

The 1969 definition of SIDS by Beckwith and colleagues has benefited innumerable families and been a focus for research that has culminated in "typical" SIDS becoming a rarity in many countries. This welcome reduction in SIDS cases has brought to the forefront problems with the definition and its overuse.

Problems arise because the definition (which is really a description) is imprecise and because the term SIDS is used in 2 different and sometimes incompatible ways. First, it is a certifiable cause of death that is also a starting point for supporting bereaved parents; second, it is an inclusion criterion for SIDS research. This dichotomy is addressed in Dr Beckwith's proposed 2-tier approach, but the imprecision is not.

A unique aspect of SIDS is that it is the only context in which a pathologist can give a certifiable cause of death in the absence of finding an explanation, pathologic or otherwise. We owe it to parents who have experienced SIDS to apply this privileged "diagnosis" carefully so that it is not clouded by the inclusion of problematic cases that later turn out not to be natural, recognizing that all grieving parents deserve support. More selective use of the term SIDS protects most parents whose babies have died naturally and is entirely in keeping with our changed legal obligation, which in many jurisdictions is to put the welfare of children before that of their parents.

Unfortunately Dr Beckwith's proposed generic definition is inevitably as imprecise as its forebears, although I agree with the generalizations on which it is based. However, it will be as difficult to apply in individual cases as its predecessors because it does not address what is most lacking in the arena of death investigation and certification; that is, a clear consensus about when it is acceptable to give a natural cause of death (SIDS) in the approximately 40% of cases of unexpected infant death when significant questions arise about accidents, inappropriate care, or even abuse. In about 5% to 10% of cases otherwise classifiable as SIDS, confidential mul-

REVIEW

Sudden infant death syndrome

Carl E. Hunt, Fern R. Hauck

Sudden infant death syndrome (SIDS) continues to be the most common cause of postneonatal infant death. SIDS is a complex, multifactorial disorder, the cause of which is still not fully understood. However, much is known now about environmental risk factors, some of which are modifiable. These include maternal and antenatal risk factors such as smoking during pregnancy, as well as infant-related risk factors such as non-supine sleeping position and soft bedding. Emerging evidence also substantiates an expanding number of genetic risk factors. Interactions between environmental and genetic risk factors may be of critical importance in determining an infant's actual risk of SIDS. Although no practical way exists to identify which infants will die of SIDS, nor is there a safe and proven prevention strategy even if identification were feasible, reducing exposure to modifiable risk factors has helped to lower the incidence of SIDS. Current challenges include wider dissemination of guidelines to all people who care for infants, dissemination of guidelines in culturally appropriate ways, and surveillance of SIDS trends and other outcomes associated with implementation of these guidelines.

CMAJ 2006;174(13):1861-9

Sudden infant death syndrome (SIDS) is defined as the sudden death of an infant under 1 year old that is unexpected by history and unexplained after a thorough postmortem examination, including a complete autopsy, investigation of the scene of death and review of the medical history.[1] Despite declines in SIDS rates of more than 50% in Canada, the United States and many other countries, SIDS continues to be the leading cause of postneonatal infant death, accounting for about 25% of all deaths between 1 month and 1 year of age.[2-4] The declines in rates are attributed in large part to educational campaigns advocating that infants be placed on their back to sleep, that an overall safe sleeping environment be provided and that other potential risk-reduction measures be taken. The SIDS rates in Canada and the United States were 0.3 and 0.6 per 1000 live births respectively in 2002, compared with rates of 0.8 and 1.3 per 1000 live births respectively in 1990 (Canada: Statistics Canada and Canadian WHO Statistical Information Services; Aurore Coté: personal communication, 2005).[2,3] There is evidence in some countries, however, that this remarkable progress is reaching a plateau. Changes in the classification of sudden unexpected deaths in infants by medical examiners, coroners and other certifiers from SIDS to the categories of asphyxia and "unknown" may be falsely reducing SIDS rates while the overall rate of death from unexpected deaths in infants remains the same.[4,5] In order to reduce SIDS rates further, it may be necessary to develop more robust campaigns or other intervention strategies that focus on all of the modifiable risk factors.

Researchers continue to investigate possible causes of SIDS and the factors associated with an increased or decreased risk of occurrence. More recently, the genetic basis of SIDS has been an emerging area of research. In this review, we summarize the pathophysiology, epidemiology and genetic risk factors as well as the interactions between genetic and environmental risk factors, with particular emphasis on newer findings. In addition, we include the new SIDS policy statement from the American Academy of Pediatrics.

Pathophysiology

There are no routine autopsy findings pathognomonic of SIDS and no findings required for its diagnosis. There are, however, some common observations.[6] Petechial hemorrhages occur in 68%–95% of cases and are more extensive than in explained causes of infant death. Pulmonary congestion is present in 89% of SIDS cases ($p < 0.001$ compared with non-SIDS deaths), and pulmonary edema in 63% ($p < 0.01$).

In autopsies performed according to a research protocol, infants who died of SIDS were found to have several identifiable changes in the lungs and other organs and in brainstem structure and function.[6,7] Nearly two-thirds of them had structural evidence (tissue markers) of pre-existing, chronic low-grade asphyxia, and other studies identified biochemical markers of asphyxia, including vascular endothelial growth factor (VEGF) in cerebrospinal fluid (CSF).[8] The mean VEGF concentration in CSF was 308 (standard deviation [SD] 299) pg/dL in SIDS cases compared with 85 (SD 83) pg/dL in non-SIDS–related infant deaths. SIDS infants have been found to have structural and neurotransmitter alterations in the brainstem, consistent with abnormalities in autonomic regulation. These brainstem findings include persistent increases in dendritic spines (indicating neuronal maturational delay) and delayed maturation of synapses in medullary respiratory centres, decreased tyrosine hydroxylase immunoreactivity in catecholaminergic neurons, and decreases in serotonin (5-HT) 1A and 2A receptor immunoreactivity.[6,7]

DOI:10.1503/cmaj.051671

Up to 60% of SIDS cases have been found to show histopathological evidence of varying degrees of hypoplasia of the arcuate nucleus, an integrative site for vital autonomic functions, and neurotransmitter studies have identified receptor abnormalities in some SIDS cases that involve several receptor types relevant to autonomic control.[9] These deficits include significant decreases in binding to kainate, muscarinic cholinergic and 5-HT receptors.

Risk factors

A number of factors, both modifiable and not, have been found to have significant associations with SIDS (Box 1). It is possible that the case–control design, used frequently in studying risk factors for SIDS, introduces unmeasured biases through both selection and participation of cases and controls.[10] However, studies using complete cohort and case series data have confirmed findings from case–control studies.[11–14] In addition, multiple logistic regression analysis of data from case–control studies does control for potential confounders to a substantial extent, albeit perhaps not always completely. Although we can never be fully sure that all possible confounders are considered in these analyses, the general consistency of findings across studies for many of the risk factors described herein strengthens their overall validity.

Sociodemographic factors

Although SIDS affects infants from all social strata, lower socioeconomic status, younger maternal age, lower maternal education level and single marital status are consistently associated with an increased risk of SIDS. In the United States, infants who are black, American Indian and Alaskan Native are 2–3 times more likely than white infants to die of SIDS, whereas Asian, South Pacific and Hispanic infants have the lowest incidence rates.[3] Rates of SIDS 5–7 times higher among indigenous peoples than in other groups have been reported in other countries.[2] Some of this disparity may be related to the higher concentration of poverty and other adverse environmental factors found in the communities with higher incidence. Despite declines in SIDS across all social and racial groups following educational campaigns, recent trends indicate that there are now even greater social and racial disparities.[11,12,15]

Infants are at greatest risk of SIDS at 2–4 months of age, with most SIDS-related deaths having occurred by 6 months. This characteristic age distribution has decreased in some countries as the SIDS incidence has declined, with occurrence of deaths at earlier ages and flattening of the peak incidence.[16,17] Similarly, the commonly found winter seasonal predominance of SIDS has declined or disappeared in some countries as the prevalence of infants sleeping in the prone position has decreased, which supports prior findings of an interaction between sleeping position and factors more common during colder months (e.g., overheating and infection).[18,19] Infant boys are 30%–50% more likely than girls to be affected.[20–22]

Pregnancy-related factors

Several pregnancy-related factors are associated with an increased risk of SIDS, which suggests a suboptimal in utero environment.[2] Studies have shown that mothers of SIDS infants generally receive less prenatal care and initiate care later in pregnancy than do mothers of living control infants.[21,23] Other pregnancy-related risk factors include low birth weight, preterm birth, intrauterine growth retardation and shorter intervals between pregnancies.[21,22,24] SIDS infants are often the second or higher-order birth child. This effect may be related to social strain in the care environment or possibly to increased risk of infection from siblings.[11]

Maternal substance use

There is a major association between intrauterine exposure to cigarette smoking and risk of SIDS. In studies comparing SIDS rates before and after risk-reduction campaigns, infants of mothers who smoked were about 3 times more likely than those whose mothers did not smoke to die of SIDS before implementation of the campaigns and 5 times more likely after the campaigns.[25] Most studies have shown that the risk of death is pro-

Box 1: Environmental factors associated with an increased risk of sudden infant death syndrome (SIDS)*

Maternal and antenatal risk factors	Infant risk factors
• Smoking	• Age (peak 2-4 mo, but peak may be decreasing)
• Alcohol use (especially periconceptionally and in first trimester)	• Male sex
• Illegal drug use (especially opiates)	• Race/ethnic background (e.g., black, Native Indian, other indigenous group)
• Inadequate prenatal care	• No pacifier ("dummy") used at bed time
• Low socioeconomic status	• Prematurity
• Low age	• Prone or side sleeping position
• Low level of education	• Recent febrile illness
• Single marital status	• Exposure to tobacco smoke
• Increased parity	• Soft sleeping surface, soft bedding
• Short interval between pregnancies	• Thermal stress/overheating
• Intrauterine hypoxia	• Face covered by bedding
• Fetal growth retardation	• Sharing bed with parents or siblings
	• Sleeping in own room rather than in parents' room
	• Colder season, no central heating

*Adapted from Hunt and Hauck.[7]

gressively greater as daily cigarette use increases, but the accuracy of self-reported cigarette use data is uncertain.[22,24,26] There may be a small independent effect of paternal smoking.[25] It is difficult to assess the independent effect of postnatal exposure to environmental tobacco smoke, because parental smoking behaviours during and after pregnancy are highly correlated.[25] An independent effect of postnatal exposure to tobacco smoke has been found in a small number of studies as well as a dose response for the number of household smokers, people smoking in the same room as the infant, cigarettes smoked and time the infant was exposed.[27–31] These data suggest that keeping the infant free of environmental tobacco smoke may further reduce an infant's risk of SIDS.

The evidence linking prenatal illegal drug use and SIDS is conflicting. Overall, the studies do link maternal prenatal drug use, especially opiates, with an increased risk of SIDS ranging from 2- to 15-fold.[2,31–35] In general, studies have not found an association between SIDS and maternal alcohol use prenatally or postnatally. In one study involving Northern Plains Indians, however, periconceptional alcohol use and binge drinking in the first trimester were associated with a 6-fold and an 8-fold increased risk of SIDS, respectively.[36] In a Dutch study, maternal alcohol consumption in the 24 hours before the infant died was associated with a 2–8-fold increased risk.[37] Siblings of infants with fetal alcohol syndrome have been reported to have a 10-fold increased risk of SIDS compared with controls.[38]

Infant sleep practices and environment

The prone sleeping position has consistently been shown to increase an infant's risk of SIDS.[39] As rates of prone sleeping have decreased in the general population, the odds ratios for SIDS among infants still sleeping prone have increased. For example, in Norway the odds ratio for SIDS among infants sleeping prone was 2.0 before an educational campaign and 11.0 after the campaign.[40] Infants at highest risk of SIDS may be those who are usually placed in another sleeping position but were placed on their stomachs for last sleep ("unaccustomed prone") or were found in the prone position ("secondary prone").[39] The unaccustomed prone position is more likely to occur in daycare or other settings outside the home and highlights the need for all infant caretakers to be educated about appropriate sleep positioning. Initial recommendations in SIDS risk-reduction campaigns considered placing an infant on his or her side to sleep to be nearly equivalent to the supine position in reducing the risk of SIDS, but subsequent studies have indicated that infants who sleep on their side are twice as likely to die of SIDS as infants sleeping supine.[41] Thus, current recommendations call for placing all infants on their back for sleep except those few with specific medical conditions, for which a different position may be justified.[39] Some newborn nursery staff still place infants on their side, which models inappropriate infant care practice to parents. Many parents and health care providers were initially concerned that supine sleeping would be associated with an increased risk of adverse consequences (e.g., difficulty sleeping, vomiting or aspiration). However, evidence suggests that the risk of regurgitation and choking is highest among infants who sleep in the prone position.[42] Infants sleeping on their backs have not been shown to have more episodes of cyanosis or apnea than infants sleeping in other positions, and reports of apparent life-threatening events decreased in Scandinavia after increased use of the supine position.[43] A US cohort study showed that infants sleeping on their back or side were not more likely than prone sleepers to have clinical symptoms or reasons for outpatient visits, and some symptoms and visits were actually less common among the supine sleepers.[44]

Soft mattresses, older mattresses and soft, fluffy bedding such as comforters, pillows, sheepskins and polystyrene-bean pillows have been associated with a 2–3-fold increased risk of SIDS.[2,20,45] Combinations of risk factors result in even higher risk; for example, prone sleeping in soft bedding has been associated with a 20-fold increased risk of SIDS.[46] Loose bedding, including heavy comforters, covering the head and face has also been associated with an increased risk.[46,47] Overheating has been associated with increased risk of SIDS based on indicators such as increased room temperature, high body temperature, sweating, and excessive clothing or bedding.[2] Some studies have identified an interaction between overheating and prone sleeping, with overheating increasing the risk of SIDS 6–10-fold only among infants sleeping in the prone position.[48,49] High external environmental temperatures, however, have not been associated with increased SIDS incidence in the United States.[50]

Several studies have implicated bed sharing as a risk factor for SIDS. Earlier case–control studies in England and New Zealand showed a 5–9-fold increased risk associated with bed sharing only among infants of mothers who smoked.[51,52] More recent studies have found that bed sharing was associated with increased risk of SIDS even if mothers did not smoke or if they breast-feed, particularly among younger infants.[22,24,53] Bed sharing has been found to be extremely hazardous when other children are in the same bed, when the parent is sleeping with an infant on a couch or other soft or confining sleep surface and when the infant is less than 4 months of age.[24,46,51,53,54] Risk is also increased with longer duration of bed sharing during the night; returning the infant to his or her own crib was not associated with increased risk.[51,54] Some authors have hypothesized potentially protective effects among infants who are bed sharing and breast-feeding based on observations from sleep laboratory studies, including improved maternal inspections, more infant arousals and less deep sleep.[55,56] However, no epidemiologic studies have reported a protective effect from bed sharing, and bed sharing hence should not be encouraged as a method of reducing SIDS risk. There is evidence that sleeping in the parents' room without bed sharing is associated with about a third the risk of SIDS compared with sleeping in a room separate from the parents.[24,51,55,57] Thus, the safest place for an infant to sleep may be in the parents' bedroom in a separate crib or bassinet.

Box 2: Genes identified in case-control studies for which the distribution of polymorphisms differed between infants who died of SIDS and control infants*

Cardiac ion channelopathies
- Sodium channel (*SCN5A*)
- Potassium channel

Promoter region of the serotinin (5-HT) transporter gene (*5-HTT*)

Autonomic nervous system development
- Paired-like homeobox 2a (*Phox2a*)
- Rearranged during transfection (*RET*)
- Endothelin-converting enzyme-1 (*ECE1*)
- T-cell leukemia homeobox (*TLX3*)
- Engrailed-1 (*EN1*)

Infection and inflammation
- Complement C4A and C4B
- Interleukin-10

*Adapted from Hunt.[76]

Infant feeding practices and exposures

The association between breast-feeding and SIDS is inconclusive, which may reflect the different ways in which breast-feeding is defined and measured.[39] Most studies demonstrated a protective effect of breast-feeding that was not present after adjusting for confounding factors, which suggests that breast-feeding is a marker for lifestyle or socioeconomic status and not an independent factor.[2] A few studies showed a reduced risk even after adjustment for potential factors, or they showed a dose response in which longer breast-feeding duration was associated with lower risk.[16,22] A recent analysis from the United States found that breast-feeding is associated with a decreased risk of postneonatal deaths overall but not with a decreased risk of SIDS.[58] Although the benefits of breast-feeding are many, data are currently inadequate to recommend it as a strategy to reduce the risk of SIDS.

Use of a pacifier has been associated with a significantly lower risk of SIDS in the majority of case–control studies when used for last or reference sleep. A meta-analysis found this reduced risk to be equal to an adjusted summary odds ratio of 0.39 (95% confidence interval [CI] 0.31–0.50).[59] A recent California study found an even lower risk associated with pacifier use during last sleep (adjusted odds ratio 0.08 [95% CI 0.03–0.21]), and reduced risk was found in all sociodemographic and risk categories examined, including breast-fed infants.[60] It is not known whether this reduction results from a direct effect of the pacifier itself or from associated infant or parental behaviours. There is increasing evidence, however, that pacifier use and dislodgement may enhance arousability of infants during sleep or help regulate autonomic control.[61,62]

Concerns have been expressed about recommending pacifiers as a means of reducing the risk of SIDS for fear of creating adverse consequences, particularly interference with breast-feeding.[63–65] However, no association between pacifier use and breast-feeding duration has been found in well-designed randomized controlled trials when the pacifier was introduced after breast-feeding was established.[59] Small increases in the incidence of otitis media and of respiratory tract and gastrointestinal illness have been reported among pacifier users compared with nonusers.[59] One study found that the risk of SIDS was increased among habitual pacifier users who did not use it for last sleep compared with those who did use it for last sleep and those who never used a pacifier.[54] This finding was not found in other studies in multivariate analysis.[59,60] The finding suggests, however, that for habitual users, pacifiers should be used consistently when placed for sleep. The Netherlands and Germany have recommended pacifier use as a way to potentially reduce the risk of SIDS.[67,68] The most recent American Academy of Pediatrics guidelines recommend pacifier use once breast-feeding has been established.[39] The Canadian Paediatric Society recommends that counselling about pacifiers be part of routine anticipatory guidance, but "until further research leads to more conclusive evidence on adverse outcomes," pacifier use should be a matter of parental choice.[64,69] The Canadian Paediatric Society also recommends that the use of pacifiers not be routinely discouraged, since the current evidence suggests a decreased risk of SIDS associated with their use.

Upper respiratory tract infections have generally not been found to be an independent risk factor for SIDS. These and other minor infections, however, may play a role in the pathogenesis of SIDS. An increased risk of SIDS, for example, has been found to be associated with illness among infants sleeping in the prone position, those heavily wrapped and those whose heads were covered during sleep.[2]

In case–control studies, fewer SIDS infants than control infants were found to have been immunized.[39] However, among immunized infants, no temporal relation between vaccine administration and death has been identified. Parents should be reassured that immunization does not present a risk for SIDS.[39]

Genetic risk factors

Sequencing the estimated 25 000 genes in the human genome has resulted in fundamental changes in our understanding of the role of specific genes in both health and disease. Genetic studies have now identified multiple ways in which infants who died of SIDS differ from healthy infants and those dying of other causes (Box 2).[70,71] Long QT syndrome is associated with sodium- and potassium-channel polymorphisms.[72] Overall, it is estimated that 5%–10% of SIDS cases are associated with a defective cardiac ion channel and hence an increased potential for a lethal arrhythmia.

Several studies have identified polymorphisms in the serotonin transporter (*5-HTT*) gene in infants who have died of SIDS.[76] Serotonin (5-HT) is a widespread neurotransmitter that affects a wide array of autonomic functions, including breathing, cardiovascular and circadian regulation. Several polymorphisms have been identified in the promoter region of the *5-HTT* gene. Compared with the S allele, the L allele in-

creases effectiveness of the promoter, resulting in reduced 5-HT concentrations at nerve endings. White, black and Japanese infants who died of SIDS were more likely than matched controls to have the L allele. There is also a negative association between SIDS and the S/S genotype. The L/L genotype has been associated with increased 5-HT transporters on neuroimaging and postmortem binding studies in SIDS infants.[75]

Genetic studies have identified mutations in SIDS infants pertinent to early embryologic development of the autonomic nervous system.[74] The 5 genes with identified mutations are listed in Box 2. Genetic differences among SIDS infants have also been reported for the complement C_4 gene: in a case–control study, SIDS infants who had a mild upper respiratory tract infection before death were more likely than SIDS infants without infection and living control subjects to have deletion of either the C_4A or C_4B gene.[76] Partial deletions of the C_4 gene in combination with a mild upper respiratory tract infection may thus increase the risk of SIDS. SIDS infants have also been reported to have polymorphisms in the gene promoter region for interleukin-10 (IL-10), an anti-inflammatory cytokine. IL-10 polymorphisms result in decreased IL-10 levels, which could lead to decreases in antibody production or increases in inflammatory cytokine production.[76]

No cost-effective way currently exists to screen for any of these genetic polymorphisms in early infancy. Indeed, except for the cardiac ion channelopathies, no specific clinical abnormality or phenotype has been delineated for the polymorphisms identified in SIDS infants. However, abnormalities one might expect from the identified polymorphisms are consistent with autopsy findings and with the physiologic studies available in young infants later dying of SIDS and in infants at increased risk of SIDS (siblings of prior SIDS infants and infants having had an apparent life-threatening event).[77,78] The observed physiologic abnormalities are indicative of deficient brainstem autonomic neuroregulation including respiratory pattern, chemoreceptor sensitivity, control of heart and respiratory rate and variability, and asphyxic arousal responsiveness. A deficit in arousal responsiveness may be a necessary prerequisite for SIDS to occur but may be insufficient to cause SIDS in the absence of other genetic or environmental risk factors.[79]

The ability to shorten the QT interval as the heart rate increases appears to have been impaired in some SIDS infants, which suggests that such infants may be predisposed to ventricular arrhythmia.[80] This is consistent with observations of cardiac channel gene polymorphisms in other SIDS cases, but there are no antemortem QT-interval data available for SIDS infants with postmortem genetic data. Infants who later died of SIDS were found to have higher heart rates and diminished heart rate variability in all sleep and waking states.[77] Some infants who later died of SIDS had deficient autonomic heart rate responses to obstructive apnea, which may have led to reduced electrical stability of the heart in response to external or endogenous stress factors.[78]

Interactions between genetic and environmental risk factors

The actual risk of SIDS in individual infants is determined by complex interactions between genetic and environmental risk factors (Fig. 1). There appears, for example, to be an interaction between prone sleeping position and impaired ventilatory and arousal responsiveness.[77] Face-down or nearly face-down sleeping does occasionally occur in prone-sleeping infants and can result in episodes of airway obstruction, but healthy infants will arouse before such episodes become life-threatening.[81] However, infants with insufficient arousal responsiveness to asphyxia would be at risk of sudden death.[79] There may also be interactions between modifiable risk factors such as use of soft bedding, prone sleeping position and thermal stress, and links between genetic risk factors such as

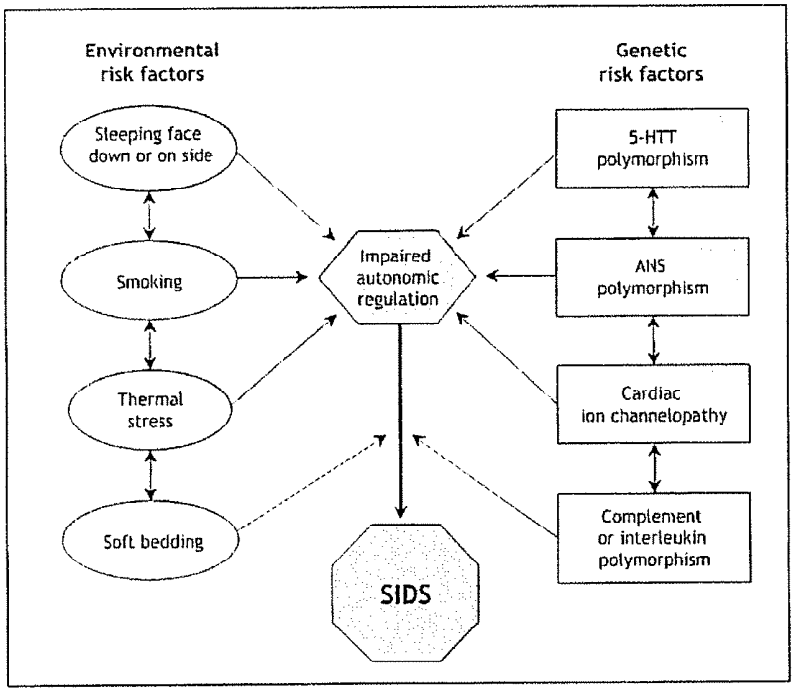

Fig. 1: Schematic summary of potential interactions between environmental and genetic risk factors for sudden unexpected death in infancy and sudden infant death syndrome (SIDS). The clinical consequences (phenotype) are not known for the autonomic nervous system and serotonin transporter (5-HTT) polymorphisms. Adapted from Hunt.[79]

ventilatory and arousal abnormalities and temperature or metabolic regulation deficits. Cardiorespiratory control deficits could be related to *5-HTT* polymorphisms, for example, or to polymorphisms in genes pertinent to the development of the autonomic nervous system. Affected infants could be at increased risk of sleep-related hypoxemia and hence more susceptible to adverse effects associated with unsafe sleeping position or bedding. Infants at increased risk of sleep-related hypoxemia and secondary acidosis could also be at increased risk of fatal arrhythmias in the presence of a cardiac ion channelopathy.[82]

Recent febrile illness, often related to upper respiratory tract infection (Box 1), has been observed in 50% or more of SIDS cases. Although not considered to be of primary etiologic significance, such otherwise benign infections could increase the risk of SIDS in infants with genetically determined impaired immune responses (Box 2).[75] Interactions between upper respiratory tract infection or other minor illnesses and other factors such as prone sleeping position may also play a role in the pathogenesis of SIDS. Mast-cell degranulation has been reported in SIDS cases, a finding consistent with an anaphylactic reaction to a bacterial toxin. Some family members of SIDS infants have been found to have mast-cell hyperreleasability and degranulation, which suggests that this may be another genetic factor influencing fatal outcomes in the presence of otherwise minor infections in infants.[77]

The increased risk of SIDS associated with fetal and postnatal exposure to cigarette smoke may be related at least in part to genetic factors affecting brainstem autonomic control.[6,77] Both animal and clinical studies have shown decreased ventilatory and arousal responsiveness to hypoxia following fetal nicotine exposure, and impaired autoresuscitation after apnea has been associated with postnatal nicotine exposure.[83–86] Decreased brainstem immunoreactivity to selected protein kinase C and neuronal nitric oxide synthase isoforms has been observed in rats exposed to cigarette smoke prenatally, another potential cause of impaired hypoxic responsiveness.[87] Smoking increases susceptibility to viral and bacterial infections and increases bacterial binding after passive coating of mucosal surfaces with smoke components, implicating interactions between smoking, cardiorespiratory control and immune status.[88,89]

Infants at increased risk of SIDS

Infants at increased risk of SIDS include those who have had an apparent life-threatening event, siblings of prior SIDS infants and infants born preterm.[6,7]

An apparent life-threatening event is defined as a sudden, unexpected change in an infant that is frightening to the caregiver but does not lead to sudden death or persistent collapse. Sudden colour change (cyanosis or occasionally marked pallor) is the most frequent observation, typically associated with initial unresponsiveness to external stimulation; apparent apnea is another frequent observation. A history of an unexplained apparent life-threatening event has been reported in 5%–9% of SIDS infants, but no definitive incidence rates are available. The risk of SIDS may be up to 3–5 times greater among infants with such a history.[6] Although most studies of apparent life-threatening events have not specified gestational age at birth, 30% of infants with such a history in the Collaborative Home Infant Monitoring Evaluation (CHIME) study had a gestational age of less than 38 weeks at birth.[90]

The next-born siblings of first-born infants dying of a natural cause have been found to be at significantly increased risk of death during infancy from the same cause, including SIDS.[70,91–93] The risk of recurrent infant death from the same cause as in the index sibling is increased to a similar degree among subsequent siblings for both explained causes and for SIDS (relative risks for recurrence 5–13 and 5–6, respectively). The extent to which the risk of SIDS may be increased in subsequent siblings is controversial, primarily because of the absence of objective criteria for ruling out intentional suffocation and to limited prior understanding of the role of genetic risk factors.[70,71] However, there are now substantial data in support of genetic risk factors for recurrent SIDS, and recent epidemiologic data confirm that second infant deaths in families are not rare and that at least 80%–90% are natural.[94] Recurrent infant death from SIDS in subsequent siblings is 6 times more likely than from homicide.

Many studies have identified an inverse relation between the risk of SIDS and birth weight or gestational age.[6] The postnatal age of preterm infants who died of SIDS was found to be 5–7 weeks more, and the postmenstrual age 4–6 weeks less, than that of term infants who died of SIDS.[95] Compared with infants whose birth weight was 2500 g or more, those with a birth weight of 1000–1499 g and 1500–2499 g were about 4 and 3 times more likely, respectively, to die of SIDS.[96]

Clinical strategies

Intervention

No method currently exists to identify future SIDS cases at birth, and there is no proven intervention even if prospective identification were feasible. No assessment of cardiorespiratory pattern or other autonomic abnormality has sufficient sensitivity and specificity to be useful for screening. There is no evidence that home electronic surveillance using existing technology reduces the risk of SIDS.[39] Although a prolonged QT interval can be treated, neither the role of routine neonatal electrocardiographic screening nor the safety of treatment has been established, and parental screening is not helpful owing to the high frequency of spontaneous mutations causing long QT syndrome in infants and to the variable presence of prolonged QT intervals in adults with a relevant genotype.[70,77]

Even though it is not possible to identify future SIDS infants at birth, it is possible to identify infants at high risk of SIDS based on combinations of established risk factors such as low birth weight, exposure to tobacco smoke, single parent, low maternal education and intent to bottle feed. Identifying high-risk infants can be the basis for targeted enhanced educational interventions to maximize adherence to recommendations for reducing the risk of SIDS.

Reducing the risk of SIDS

This goal is achievable, as evidenced by the dramatic decreases in SIDS rates associated with reductions in prone and side sleeping positions and other modifiable risk factors. The new American Academy of Pediatrics (AAP) guidelines to reduce the risk of SIDS in individual infants are appropriate for most infants.[3] The main components are summarized in Box 3.

The recommendations of the Canadian Paediatric Society (CPS) are very similar, the main exception being pacifier use.[4] The CPS recommends that the use of pacifiers not be routinely discouraged, rather than encouraged, at bedtime. It also recommends that pacifiers continue to be used in neonatal intensive care units for non-nutritive sucking and comfort in the preterm or sick infant.

Recommendations about bed sharing have been controversial. The CPS and AAP have similar recommendations about bed sharing and room sharing: infants should sleep in safety-approved cribs for the first year of life under all circumstances, and parents should be made aware that room sharing is associated with lower SIDS rates.[3,4] The CPS also recommends that hospitals not permit mothers to sleep in the same bed as their newborn during the postpartum period, while still ensuring maternal–infant interaction for successful breast-feeding initiation.

Because the majority of these recommendations are based on findings from observational studies rather than on evidence from randomized clinical trials, the effects of the newer guidelines remain to be seen. However, we support the AAP recommendations, since they are based on sound data and absence of any evidence of potential harm and are therefore likely to be effective.

Summary

SIDS is a complex, multifactorial disorder for which continued research is needed to fully understand the relevant interactions between genetic and environmental risk factors that affect causation. In the meantime, epidemiologic evidence and interventions based on this research have helped to reduce the incidence of SIDS. Current challenges include wider dissemination of guidelines to all people who care for infants, dissemination of guidelines in culturally appropriate ways, and the surveillance of SIDS trends and other outcomes associated with the implementation of these guidelines.

Box 3: Main components of the American Academy of Pediatrics guidelines to reduce the risk of sudden infant death syndrome (SIDS)

- Term and preterm infants should be placed on their back to sleep. There are no adverse health outcomes from a supine sleeping position. Infants should not be placed on their side to sleep.
- Infants should sleep in their own crib or bassinet that conforms to the safety standards of the Consumer Product Safety Commission, preferably in the same room as their parents. Placing the crib or bassinet near the mother's bed will facilitate breast-feeding and contact. Infants should never be placed in a bed or on a sofa or chair with other children. They should not be brought into bed with parents who are excessively tired or are using substances that may impair their alertness.
- Infants should be placed on a firm mattress to sleep. Waterbeds, sofas, soft mattresses or other soft surfaces should not be used.
- Soft materials in the infant's sleep environment should be avoided, either over, under or near the infant. These include pillows, comforters, quilts, sheepskins, cushion-like bumper pads and stuffed toys. Because loose bedding may be hazardous, blankets, if used, should be tucked in around the crib mattress. Sleep clothing, such as a sleep sack, may be used in place of blankets.
- Avoid overheating and overbundling. The infant should be lightly clothed for sleep and the thermostat set at a comfortable temperature.
- Infants should have some time in the prone position while awake and be observed. Alternating the placement of the infant's head as well as his or her orientation in the crib can also minimize the risk of head flattening from supine sleeping (positional plagiocephaly).
- The use of devices advertised to maintain sleep position, to "protect" a bed-sharing infant or to reduce the risk of rebreathing stale air are not recommended.
- Home monitoring may be of value for selected infants who have extreme instability. However, there is no evidence that monitoring decreases the incidence of SIDS, and it is therefore not recommended for this purpose.
- Consider the use of a pacifier at bedtime and naptime. The pacifier should be used when placing the infant down for sleep but not be reinserted once it falls out (after the infant falls asleep). For breast-fed infants, delay the introduction of a pacifier until the infant is 1 month old, to ensure that breast-feeding is well established.
- Mothers should not smoke during pregnancy, and infants should not be exposed to secondhand smoke.
- The national Back to Sleep campaign should be expanded to emphasize the multiple characteristics of a safe sleeping environment and to focus on the groups who continue to be at increased risk of SIDS. Educational strategies should be tailored to each racial/ethnic group to enhance compliance. In addition, these educational messages should be targeted to secondary care providers, including day-care providers, grandparents, foster parents, babysitters and health care professionals working in neonatal intensive care units and nurseries.

This article has been peer reviewed

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Competing interests: None declared

Contributors: Both authors made a substantial contributions to conception and design, acquisition of data, and interpretation of data; contributed to writing drafts of the article and revising it critically for important intellectual content; and approved the final version to be published

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Pathology Research Into Sudden Infant Death Syndrome: Where Do We Go From Here?

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Pediatrics 2004;114;492-494
DOI: 10.1542/peds.114.2.492-a

Journeys From Childhood to Midlife: Risk, Resilience, and Recovery

The latest report from the Kauai Longitudinal Study addresses 2 fundamental questions of interest to pediatricians and health care professionals: 1) What are the long-term effects of adverse perinatal and early child-rearing conditions on individuals' physical, cognitive, and psychosocial development at midlife? 2) Which protective factors allow most individuals who are exposed to multiple childhood risk factors to make a successful adaptation in adulthood?[1]

The Kauai Longitudinal Study has monitored the impact of a wide array of biological, psychological, and social risk factors on the lives of a multiracial cohort of 698 individuals who were born in 1955 on the Hawaiian island of Kauai, from the perinatal period to ages 1, 2, 10, 18, 31/32, and 40. The follow-up at midlife was able to track ~80% of the "high-risk" children who had been exposed to chronic poverty, birth complications, parental psychopathology, and family discord (approximately one third of the cohort) as well as comparison groups of men and women who had not experienced significant childhood adversities.

With the exception of serious central nervous system damage, the impact of perinatal complications on adult adaptation diminished with time, whereas the outcomes of biological risk conditions depended, increasingly, on the quality of the child-rearing environment and the emotional support provided by family members, friends, teachers, and adult mentors. Most of the high-risk youths who had developed serious coping problems in adolescence (learning disabilities, mental health problems, teenage pregnancies, and/or a record of delinquencies) had staged a recovery by the time they reached the end of their fourth decade of life. Overall, such "troubled" teenagers had a slightly higher mortality rate by age 40 than did the cohort as a whole, but the majority of the survivors were in stable marriages and jobs, were satisfied with their relationships with their spouses and children, and were responsible citizens in their community.

Poorest outcomes at age 40 were associated with prolonged exposure to parental alcoholism and/or mental illness—especially for the men. Individuals who had been born small for gestational age and those who received a diagnosis of mental retardation in childhood had a higher incidence of serious health problems in adulthood, including serious depression. They also had higher mortality rates than was the norm for men and women of their age. Men and women who had encountered more stressful life events in childhood reported more health problems at age 40 than those who had encountered fewer losses and less disruption in their family during the first decade of life.

Health status in the first decade of life (based on a pediatric assessment of all organ systems at age 2 and number of health problems, including serious illnesses and accidents, between birth and age 10) correlated significantly with the quality of the individual's adaptation at age 40—as did the mother's caregiving competence and the emotional support provided by the family in childhood.

This study demonstrates the need for early attention to the health status of our nation's children—especially those who are exposed to poverty, serious perinatal complications, and parental psychopathology. The social policy implications are clear: early access to good preventive and ameliorative health services and proper attention to the quality of early child care can pay ample dividends in an improved quality of life in adulthood.[2]

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Received for publication Jan 21, 2004; accepted Feb 2, 2004
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PEDIATRICS (ISSN 0031 4005)

Pathology Research Into Sudden Infant Death Syndrome: Where Do We Go From Here?

ABBREVIATION. SIDS, sudden infant death syndrome.

Epidemiologic research into sudden infant death syndrome (SIDS) has resulted in the recognition of factors that place an infant at increased risk of SIDS. The avoidance of these risk factors promulgated through public education programs, such as the "Reduce the Risk" campaign in Australia, New Zealand, and Western Europe as well as the "Back to Sleep" campaign in the United States, led to astounding reductions in SIDS rates in these communities.[1]

Although these risk factors may provide clues to causation, the ultimate clarification of the mechanisms of death in SIDS will require basic research in pathology. For example, prone sleep position is a

Received for publication Dec 19, 2003; accepted Dec 19, 2003
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PEDIATRICS (ISSN 0031 4005)

very important risk factor for SIDS, but its role in the cause of death remains an enigma. External airway obstruction,[2,3] rebreathing into soft sleep surfaces,[4–6] hyperthermia,[7] and increased frequency of mild infectious symptoms combined with a stimulated mucosal immunoglobulin A system of the larynx, inducing release of cytokines in the brain,[8–11] are among a number of proposed but not universally accepted mechanisms of death in SIDS infants who are found prone. The reduction of serotonergic, kainate, and muscarinic cholinergic neurotransmitter receptors in a subset of SIDS cases has also been proposed to link prone sleep position and sudden death.[12–14] Similarly, the explanation of the relationship between SIDS and other risk factors, including premature birth, low birth weight, and smoke exposure, awaits new research into basic pathology. Answers to these questions await a new research using very sophisticated methods into the pathology of postmortem specimens from these infants.

Unfortunately, research in a number of countries, including the United Kingdom and Australia, has been dramatically reduced as a result of recent events involving retention of postmortem specimens. Some of the most important current research into SIDS depends on postmortem specimens. Delay or improper processing of these specimens will diminish or preclude their value for research purposes. The dramatic decline in rates has also resulted in a reduction of SIDS cases available for research purposes. Both of these factors conspire to prevent parents who are the most motivated to understand why their infants died from getting answers to their questions.

Given this impasse, where do we go from here? It seems to us that the parents of infants who die of SIDS and investigators who partner together hold the key to future research in pathology. A suggestion that we strongly support is that together, they should advocate for statutory authorization to use these specimens legally for research without having to obtain consent from each individual family. There is precedent for this. In California, parents of infants who die of SIDS were the driving force for legislation that authorized research using postmortem specimens of infants who had died suddenly. In collaboration with investigators, these bereaved yet visionary parents helped to write the senate bills, lobbied their legislators, testified before government committees, and assisted in the creation of standardized protocols for scene investigation and postmortem examination. Without their commitment and support, some of the most important SIDS research during the past decade could not have taken place. It seems that broadening this experience beyond California is a reasonable goal.

How can this be accomplished? Investigators need to communicate these research-related issues to the SIDS parent community. Just as collaboration of SIDS researchers with national parent education programs that address infant care produced stunning and significant reductions in SIDS rates, we believe that the collaboration of parents and investigators can result in legislation that authorizes research using postmortem specimens. The methods used in these studies often depend on postmortem specimens that are collected and processed as soon as possible after death to yield credible and reproducible results. It is because of this that seeking authorization on a case-by-case basis is often impractical and will lead to a reduction of useful specimens for research purposes. There are many SIDS organizations, composed of parents of infants who died of SIDS, that can serve as an interface between newly bereaved survivors and legislative bodies and research laboratories.

We should emphasize that we understand that retaining postmortem specimens may be in potential conflict with religious beliefs, cultural mores, and personal attitudes. Recruitment of religious scholars and ethicists to assist parents, researchers, and legislators may help to facilitate achieving acceptable compromises. Public lectures and more informal workshops with smaller groups are undertakings that have assisted parents in understanding issues that researchers confront. These activities serve to demystify the scientific method and to allow parents to be more informed and involved in studies that have extreme emotional significance to families. Dialogue between researchers and parents will only serve to strengthen SIDS research and circumvent some of the unnecessary and destructive episodes that have damaged considerably what has in the past been a very fruitful and harmonious collaboration.

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Closing the Gap Between Guidelines and Practice: Ensuring Safe and Healthy Beginnings

ABBREVIATIONS. AAP, American Academy of Pediatrics; ADHD, attention-deficit/hyperactivity disorder.

Once you bring life into this world you must protect it. We must protect it by changing the world.

Elie Weisel

The revised American Academy of Pediatrics' (AAP's) guideline for the management of hyperbilirubinemia in infants ≥35 weeks' gestation,[1] published in the July issue, provides a contemporary evidence-based approach to a condition that affects the majority of otherwise healthy newborns. Adherence by clinicians to the recommendations is expected to prevent most cases of kernicterus, the devastating, irreversible neurologic damage associated with excessive serum levels of bilirubin.

Despite the publication of a previous version of the guideline in 1994, kernicterus continues to occur.[2] Many contributing factors may be at play. For example, the change to early discharge, often at <48 hours after birth, disrupted the previous patterns of care associated with a longer postpartum hospitalization.[3] As a result, newborns now experience the usual peak of serum bilirubin concentration, at 3 to 5 days of age, at home rather than observed by clinicians in the nursery as in previous times. This change in clinical venue also contributes to gaps in communication, continuity, and parent education. Discharge now generally occurs before lactation is well established and often without adequate support, further increasing the risk of hyperbilirubinemia. Furthermore, follow-up visits are scheduled at a median of 1 week of age, later than would be optimal for assessment of jaundice and lactation.[4] Another factor may be the current state of laissez-faire "jaundice-related thinking" among pediatricians and the health care community. One author suggested that because most pediatricians and family practitioners have never seen a case of kernicterus first hand, they commonly adopt a "not to worry" attitude.[5] Finally, insurance policies do not always facilitate appropriate care for infants. These include lack of support for a prenatal visit with an infant health care provider, no reimbursement for transcutaneous bilirubin measurement, and lack of routine coverage for systematic follow-up by a clinician.[3]

THE CHALLENGE OF TRANSLATING EVIDENCE INTO PRACTICE

Although guidelines provide an evidence-based approach, they frequently fail to translate into standard practice and improved care. Why is this? Multiple studies of strategies used to change practice demonstrate that the passive provision of information, as in traditional didactic continuing medical education, rarely achieves its intended goal.[6–9] Knowledge is essential but not sufficient to produce behavior change.[10,11]

Interventions that are based on assessment of potential barriers and multifaceted interventions that target different barriers to change are more likely to be effective than single interventions in changing practice or improving health outcomes.[6–8] In particular, activities that seem to have a positive effect include those with active learning opportunities, learning delivered in a longitudinal or sequenced manner, and the provision of methods to facilitate implementation in the practice setting (eg, tools and resources).[7] In addition, theories of the spread of innovations suggest that changes in practice disseminate more rapidly when they can be simplified so that limited adaptation is required. The use of simple tools and practical strategies that can help clinicians to make the transition from current processes to newer approaches is more likely to be successful in improving care and outcomes.[12,13]

A FRAMEWORK FOR TRANSLATING POLICY INTO PRACTICE

Successful efforts to improve care recognize that multiple layers of the health care system need to work together to achieve better outcomes (Fig 1). The American Academy of Pediatrics (AAP) used this framework in developing its multifaceted program to translate the guidelines for the diagnosis and treatment of attention-deficit/hyperactivity disorder (ADHD) into clinical practice. The ADHD effort consists of a several-year program of coordinated activities targeting the various levels of the health care system: advocacy efforts to dismantle financial and organizational obstacles to promote timely access to care in the medical home setting, structured educational efforts to support improved care in AAP chapters and residency programs, a toolkit and Web-based continuing medical education/quality improvement program for clinicians (the AAP's Education for Quality Improvement in Pediatric Prac-

Received for publication Apr 21, 2004; accepted Apr 29, 2004
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Pathology Research Into Sudden Infant Death Syndrome: Where Do We Go From Here?

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Pediatrics 2004;114;492-494
DOI: 10.1542/peds.114.2.492-a

Sudden Infant Death Syndrome and Unclassified Sudden Infant Deaths: A Definitional and Diagnostic Approach

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ABSTRACT. The definition of sudden infant death syndrome (SIDS) originally appeared in 1969 and was modified 2 decades later. During the following 15 years, an enormous amount of additional information has emerged, justifying additional refinement of the definition of SIDS to incorporate epidemiologic features, risk factors, pathologic features, and ancillary test findings. An expert panel of pediatric and forensic pathologists and pediatricians considered these issues and developed a new general definition of SIDS for administrative and vital statistics purposes. The new definition was then stratified to facilitate research into sudden infant death. Another category, defined as unclassified sudden infant deaths, was introduced for cases that do not meet the criteria for a diagnosis of SIDS and for which alternative diagnoses of natural or unnatural conditions were equivocal. It is anticipated that these new definitions will be modified in the future to accommodate new understanding of SIDS and sudden infant death. *Pediatrics* **2004;114: 234–238; *SIDS, sudden infant death.***

ABBREVIATION. SIDS, sudden infant death syndrome.

Sudden infant death syndrome (SIDS) is a term that has been used to describe unexpected deaths of infants or young children when subsequent investigations fail to demonstrate a definite cause of death.[1,2] The concept, which was first proposed in 1969, has been controversial, and its use has been characterized by great variability in the consistency with which the requirements of standard definitions have been fulfilled.[3–5] Specifically, the term has been overused and applied to cases in which there have been obvious natural or unnatural causes of death; also, the term has been underused in favor of imprecise terms such as undetermined or unascertained. A number of other definitions that have included quite different criteria have been proposed.[6–9] The most widely used definitions have made SIDS a diagnosis of exclusion.

In 1969, at the Second International Conference on Causes of Sudden Death in Infants, it was proposed that SIDS was "the sudden death of any infant or young child which is unexpected by history, and in which a thorough postmortem examination fails to demonstrate an adequate cause of death."[1] In 1989, the National Institute of Child Health and Human Development convened an expert panel to reexamine the issue of definition. The panel proposed that SIDS was "the sudden death of an infant under 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."[2,8,9,11] This definition limited the age to <1 year and specified that a thorough examination should include examination of the death scene and review of the clinical history.

In 1992, at the SIDS International Meeting in Sydney, Australia, Bruce Beckwith proposed stratification of the definition to enable separation of cases into typical and atypical groups.[4] The proposal was not accepted at the time, although others subsequently supported subclassification.[10] In 2003, Beckwith again called for a reexamination of the definition of SIDS, with the possibility of including positive diagnostic criteria and stratification to delineate particular subsets.[11] As a result of this proposal, a meeting was held in San Diego, California, in January 2004; it was sponsored by the CJ Foundation for SIDS and involved an invited panel of experts, including pediatric pathologists, forensic pathologists, and pediatricians, all of whom had extensive experience with sudden infant death. Delegates came from Europe, North America, and Australasia.

DISCUSSION POINTS

Presentations on a variety of topics were made first. Bruce Beckwith (Loma Linda University, Loma Linda, CA) discussed the history of SIDS definitions,

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Received for publication Mar 1, 2004; accepted May 3, 2004.

Report of an expert panel convened by the CJ Foundation for SIDS, San Diego, California, January 9–11, 2004 (moderator: Henry F. Krous).

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PEDIATRICS (ISSN 0031-4005).

the present status, and possible proposals for the future. He indicated that the meeting represented an attempt to formulate an approach to sudden infant death that would clarify subsets and assist research but that it was a work in progress that would need to be revisited regularly. Data presented from Seattle in the 1960s and 1970s demonstrated that 95% of SIDS cases were within the age range of 1 to 6 months. Edwin Mitchell (University of Auckland, Auckland, New Zealand) also discussed the need for redefinition and the possible place of risk factors in a new definition. He pointed out that, although specific risk factors were consistent across studies, the prevalence varied among countries; therefore, he considered it better to leave risk factors out of definitions. Mitchell emphasized the importance of researchers defining their study populations carefully. Henry Krous (Children's Hospital San Diego, San Diego, CA) presented data from the San Diego study on the frequency of risk factors and the changes that have occurred since the Back to Sleep campaigns, specifically the decrease in the winter peak and the proportionate increase in the number of cases < 1 month of age. Torleiv Rognum (University of Oslo, Oslo, Norway) discussed the need for a new definition and particular problems with SIDS because of its uneasy position between the health system and the legal system. Data from Oslo in the 1980s showed an age distribution similar to the Seattle results; in later years, however, there was a decrease in the number of cases 2 to 4 months of age, with increases in the numbers of cases involving younger and older infants. When cases ≥360 days of age were excluded from the latter cohort, however, the distribution of cases was similar to data from Seattle before the Back to Sleep program. Randy Hanzlick (Fulton County Medical Examiner's Center, Atlanta, GA) discussed the advantages and disadvantages of reporting on the death certificate, or in other SIDS databases, those risk factors that might have been operative in causing or contributing to death, emphasizing that reporting such conditions might enable better tracking through official documentation. Hanzlick suggested that the group discuss the merits of abandoning the term SIDS and replacing it with "sudden unexplained infant death." Problems with the use and scope of the *International Classification of Disease* coding were reviewed, including sometimes-inadequate specificity, overlap, and variable application among coders. Roger Byard (Forensic Science Centre, Adelaide, Australia) discussed the use of the terms undetermined and unascertained in flagging cases in which significant parts of the investigation were lacking or in which there were questions regarding possible causes of death. Byard also warned against the indiscriminate use of these terms to cover inadequate autopsy and case investigations.

A group discussion followed, during which the advantages of formulating and promulgating a redefinition of SIDS were actively debated. It was agreed that creating and supporting a more inclusive SIDS definition would facilitate uniformity in diagnosis, with a resultant increase in information on current cases. It would also enable accumulated data to be better used and would provide opportunities to propose and evaluate new theories, particularly regarding possible SIDS subsets. Existing SIDS definitions were considered inadequate, often being applied too generally or too restrictively, and were exclusionary, failing to incorporate known features of the syndrome (such as sleep and age range). The conclusions of the group were based on assessments of current trends and data and were intended to be fully reevaluated in the future, when they will likely need to be modified to accommodate new developments.

The redefinition was also considered a useful step to enable more precise monitoring of changing epidemiologic patterns in sudden infant deaths and to allow more valid international comparisons. By more clearly defining subsets of sudden infant deaths, monitoring of the effects of public health recommendations and alterations in infant care practices can be facilitated. Finally, more precise definitions of subsets of sudden infant deaths, with specification of requirements for diagnosis, should help standardize investigative protocol development, by improving examinations of the circumstances of death and autopsy investigations and bringing investigations more in line with recommended guidelines.[12–14] Providing more information and more rigorous subclassification of cases should also facilitate integrated multiagency approaches to such cases.[7]

RESULTS

Definitional Approach to Sudden Infant Death

The following definition and subclassification were agreed upon.

General Definition of SIDS

SIDS is defined as the sudden unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history.

Category IA SIDS: Classic Features of SIDS Present and Completely Documented

Category IA includes infant deaths that meet the requirements of the general definition and also all of the following requirements.

Clinical

- More than 21 days and <9 months of age
- Normal clinical history, including term pregnancy (gestational age of ≥37 weeks)
- Normal growth and development
- No similar deaths among siblings, close genetic relatives (uncles, aunts, or first degree cousins), or other infants in the custody of the same caregiver

Circumstances of Death

- Investigation of the various scenes where incidents leading to death might have occurred and determination that they do not provide an explanation for the death

- Found in a safe sleeping environment with no evidence of accidental death.

Autopsy

- Absence of potentially fatal pathologic findings. Minor respiratory system inflammatory infiltrates are acceptable; intrathoracic petechial hemorrhage is a supportive but not obligatory or diagnostic finding.
- No evidence of unexplained trauma, abuse, neglect, or unintentional injury
- No evidence of substantial thymic stress effect (thymic weight of <15 g and/or moderate/severe cortical lymphocyte depletion). Occasional "starry sky" macrophages or minor cortical depletion is acceptable
- Negative results of toxicologic, microbiologic, radiologic, vitreous chemistry, and metabolic screening studies.

Category IB SIDS: Classic Features of SIDS Present but Incompletely Documented

Category IB includes infant deaths that meet the requirements of the general definition and also meet all of the criteria for category IA except that investigation of the various scenes where incidents leading to death might have occurred was not performed and/or ≥1 of the following analyses was not performed: toxicologic, microbiologic, radiologic, vitreous chemistry, or metabolic screening studies

Category II SIDS

Category II includes infant deaths that meet category I criteria except for ≥1 of the following.

Clinical

- Age range outside that of category IA or IB (ie, 0–21 days or 270 days [9 months] through first birthday).
- Similar deaths among siblings, close relatives, or other infants in the custody of the same caregiver that are not considered suspect for infanticide or recognized genetic disorders
- Neonatal or perinatal conditions (for example, those resulting from preterm birth) that have resolved by the time of death

Circumstances of Death

- Mechanical asphyxia or suffocation caused by overlaying not determined with certainty.

Autopsy

- Abnormal growth and development not thought to have contributed to death
- Marked inflammatory changes or abnormalities not sufficient to be unequivocal causes of death.

Unclassified Sudden Infant Death

The unclassified category includes deaths that do not meet the criteria for category I or II SIDS but for which alternative diagnoses of natural or unnatural conditions are equivocal, including cases for which autopsies were not performed

Postresuscitation Deaths

Infants found in circumstances who are resuscitated and later die (temporarily interrupted SIDS) may be included in the aforementioned categories depending on the fulfillment of relevant criteria.

DISCUSSION

Before the meeting, participants were asked to submit their own definitions of SIDS. From this pool, a common definition that incorporated agreed-upon points was formulated. Although in previous definitions SIDS was a diagnosis of exclusion, it was recognized that there were certain repetitive features common to the majority of cases. It was these features that led early investigators to suggest that most, but not all, sudden unexplained postneonatal deaths represent a distinct syndrome, reflecting a common cause or more likely, a common mechanism of death. The elements of this presumptive syndrome were ignored during formulation of the previous exclusion-based definitions, however. Major features emphasized in early SIDS studies included an association with sleep and a relatively narrow age range and frequency distribution, sparing the first weeks of extrauterine life, peaking during the 2nd to 4th months, and declining rapidly thereafter. Deaths with onset while awake are rare and most probably involve a different mechanism of death, compared with classic SIDS deaths.[7] A general definition that involved these specific criteria was created, to include as many cases as possible in the SIDS classification. This was thought to be useful for certification purposes and also for general epidemiologic studies. The phrase "death scene examination" was changed to "review of the circumstances of death," with the aim of encouraging more comprehensive assessments of the events surrounding death. For example, although an infant's death may occur in a hospital after attempted resuscitation and thus the scene is technically an emergency department, the circumstances involve the crib, room, and house where the infant was found. Review of the circumstances of death includes not only examination of the death scene but also assessment of all of the environments an infant might have been in before or after death.

After implementing a broad overall definition, participants decided to subcategorize SIDS cases on the basis of specific epidemiologic features and the amount of information available. This was prompted partly by the knowledge that the number of classic SIDS cases, typical of those occurring in the 1970s and 1980s (before the Back to Sleep and Reduce the Risks campaigns), had decreased and it was likely that the remaining cases represented a relatively more heterogeneous group, with varied underlying mechanisms of death.

Stratification of cases of sudden infant death into subcategories was therefore undertaken to:

- Provide recommended guidelines for general case assessment, classification, and diagnosis.
- Assist pathologists by detailing steps for infant death investigation and diagnostic categorization

- Identify and include cases that recently have been excluded incorrectly from SIDS groups because of findings of bed-sharing and prone sleeping position.
- Formalize current practices among pathologists of separating cases on the basis of the degree of certainty and the confidence with which a diagnosis of SIDS can be made.
- Reduce diagnostic confusion by introducing uniform terms.
- Provide a framework for researchers and identify the most typical cases for study.
- Assist in the evaluation of published data.
- Provide a readily accessible categorization of SIDS cases on the basis of age groups and investigative information.

Dividing cases of sudden infant death that fit the general definition of SIDS into subgroups should not have an effect on epidemiologic studies of the syndrome as a whole, because most cases would still be classified as SIDS. However, researchers looking for classic SIDS cases to study could take them from category IA. The group considered it important that researchers specify which subgroups were used for studies, because that would enable immediate assessment of the rigor with which cases had been investigated and determination of how closely the study group represented classic SIDS cases. It was also recommended that future research should be undertaken to examine similarities and differences among the subgroups, which might clarify specific causes.

The age range of 3 weeks to 9 months was chosen on the basis of an analysis of data from the Avon and Confidential Enquiry Into Stillbirths and Death in Infancy studies in the United Kingdom, New Zealand Health Information Services data, the Chicago and San Diego SIDS studies in the United States, studies at the Rett-medisinsk Institutt in Oslo, Norway, and the Westphalian and German Sudden Infant Death studies in Germany, by Edwin Mitchell. Pooling of data from those studies showed that the 5th to 95th percentile limits for SIDS deaths were ~3 weeks to 9 months.

Prone position was considered an established risk factor for SIDS deaths but not a cause of suffocation unless specific circumstances (such as a face-down position on an incompletely filled waterbed or in a thin plastic bag) could be demonstrated. For this reason, infants found prone with no evidence of suffocation could be included in any of the categories, depending on other features. Prone sleeping involves an array of potential problems, including diaphragmatic splinting/fatigue, rebreathing of carbon dioxide, reflex lowering of vasomotor tone with tachycardia, blunting of arousal responses (including decreased cardiac responses to auditory stimulation), alteration of sleep patterns, upper airway obstruction resulting from soft bedding, and overheating, and is most likely a problem only among infants with underlying susceptibilities.[17] Similarly, although there is evidence of increased risk of infant death in shared sleeping situations,[18] shared sleeping does not automatically exclude SIDS as a possibility if it can be shown that the infant was not at risk of accidental asphyxia. It should be recognized that the position in which the infant is found sometimes reflects agonal movement and is not necessarily the position of the infant at the onset of the fatal event.

It was acknowledged that a number of different and variably defined terms were being used to classify unexpected infant deaths. Sudden unexpected death in infancy is a general term that covers SIDS and other types of unexpected infant deaths. When an infant dies suddenly and unexpectedly and intentional or unintentional fatal injury can be excluded, death may be attributable to a specific disease entity, such as myocarditis, or to SIDS.[19] Deaths that cannot be precisely subcategorized or classified have been deemed undetermined, undeterminable, unascertained, or unascertainable, but this has created concerns about the specificity of these terms. The merits of replacing the term SIDS with sudden unexplained infant death were briefly discussed during the meeting, but it was the consensus of the group that SIDS still served a useful purpose. The term unclassified sudden infant death was proposed to account for cases in which the criteria for category I or II SIDS were not met or an autopsy was not performed. These cases may represent SIDS deaths, but there is insufficient information available to make that judgment or there are certain atypical features, such as inflicted but nonlethal injury, that are insufficient by themselves to establish a cause of death but are thought to preclude use of the term SIDS. Atypical features may also include underlying organic diseases, such as an anomalous coronary artery without evidence of myocardial ischemia, which may also preclude a confident statement about a possible cause of death.

The investigation of infant deaths should be conducted according to established protocols[20-23] and should include careful evaluation of the death scene, external examination of the body with photographic documentation, radiologic examination, internal examination with photographic documentation, and histologic, microbiologic, toxicologic, biochemical/metabolic screening, and genetic studies if indicated. Guidelines for and confirmation of the usefulness of such stepwise examinations are available in the literature.[21-23]

Finally, it should be reiterated that these proposals represent nothing more than attempts to improve definitions and to facilitate more accurate investigation, diagnosis, and categorization of cases of unexpected infant death. Considerable public, professional, and media attention has been paid recently to certain high-profile court cases in which the standards of investigation and pathologic analyses were far from acceptable. This does not mean that the underlying concepts are flawed; rather, it means that diagnostic terms and protocols should be more rigorously defined and standard investigative approaches should be maintained. The proposed framework is a work in progress, which will need to be continually reformulated and refined as more knowledge becomes available and our understand-

ing of these complex and challenging cases becomes clearer. (At a pathology workshop in Canberra, Australia, in March 2004, forensic and pediatric pathologists representing forensic institutions and hospitals from all Australian states and territories unanimously endorsed the new general San Diego definition and recommended its national implementation.)

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