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I was privileged to attend the 9th *SIDS International Conference* in Yokohama, Japan, June 1-4, 2006. The Conference was extremely well organized by our Japanese hosts. Over 500 people attended the Conference from all over the world, including SIDS parents, SIDS Program Professionals, and SIDS researchers. In addition, the *International Stillbirth Alliance* joined the SIDS International Conference for the first time. The venue was the harbor-side in Yokohama, which is an upbeat entertainment area with luxurious hotels and amusement park entertainment. The Conference was dedicated to the memory of the great Belgian SIDS Researcher, *Andre Kahn*. To the best of my knowledge, the Californians who attended the conference were: Ron Harper, Tom Keens, Henry Krous, and Sharon Lang.

SIDS Epidemiology Researchers



Peter Fleming and Peter Blair, U.K.



Fern Hauck, U.S.A.



Ed Mitchell, New Zealand



Ian Mitchell, Canada.



Rachel Moon, U.S.A.



H. Nishida, Japan



Anat Shatz, Israel

Regrettably, I arrived late on the evening of the first day (June 1, 2006), but in time to attend the Memorial Service (in fact, they were aware when my plane landed and that I was on the way, so they kept the buses waiting for me). The Memorial Service was unique and spectacular, and unlike anything I have experienced at other SIDS Conferences. We were taken by bus ~30-minutes from Yokohama to the Sojiji Buddhist Temple. The Memorial Service was in the main temple. Nearly 100 Buddhist monks filed in and sat chanting Buddhist scriptures. The

chanting was not complex musically, but it was very stirring. And it formed the perfect background for everyone in the room (probably 200-300 people) walking up to the altar, and putting a handful of incense into burning incense pots. Each handful caused the incense to smoke and flame, sending each person's thoughts, wishes, memories, and hopes heavenward. I found it to be a very moving

ceremony, and a powerful start to the four day Conference. This was followed by a traditional Zen (vegetarian) meal --- mostly tempura style food, and an opportunity to try meditation in the traditional Japanese way. I was terrible at that. I can not sit still that long, and my feet were falling asleep. Nevertheless, it was a fascinating

First thing in the morning of June 2, 2006, I attended the Annual Meeting of the *International Society for the Study and Prevention of Infant Deaths (ISPID)*, the international society for SIDS researchers. As an aside, I was nominated to run for a seat on the ISPID Board of Directors, but I lost the election by 10 votes. Peter Fleming (U.K.) beat me, so I can't really complain. The big issue was the potential merger of ISPID with SIDS International, to form one unified organization for SIDS. After much debate, a model of complete unification was overwhelmingly agreed upon, and ISPID will work with SIDS International to make this a reality.

ISPID-SIDS International Merger



Debra Boyd, USA
President, SIDS International



Martin Schlaud, Germany
President, ISPID

You could not attend everything at this SIDS Conference. There were several tracks.

- SIDS Parents.
- SIDS Program Professionals
- SIDS Researchers
 - Physiology
 - Pathology
 - Epidemiology
- International Stillbirth Alliance.

I chose to attend the Physiology sessions in the SIDS Research track. Therefore, I can not give you a complete account of all the exciting things which happened in Yokohama. However, the presentation on the new American Academy of Pediatrics Risk Reduction Recommendations, by Fern Hauck and Rachel Moon, was controversial. As in the U.S., Japanese breast-feeding advocates came out against the room sharing, but not bedsharing, and pacifier recommendations.

Let me try to summarize my synthesis of the current thinking about causes and mechanisms of SIDS, as discussed primarily in the Physiology Research sessions at Yokohama. The cause of SIDS is not known. There are no tests that can be performed on living infants,



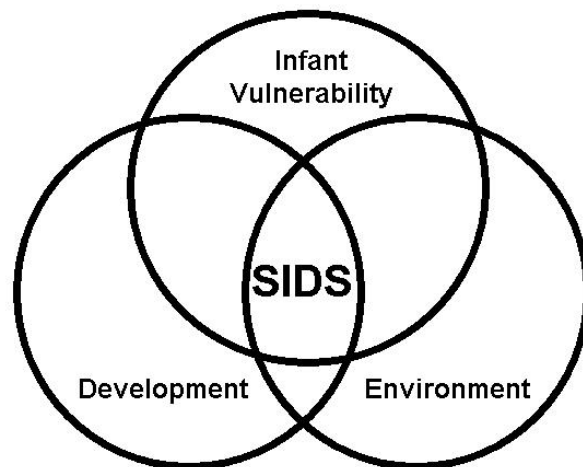
Rachel Moon, Tom Keens, and Fern Hauck.

which will predict SIDS. SIDS appears to be the result of a natural process. SIDS deaths did not occur because of something SIDS parents did or failed to do. SIDS is probably not as simple as one abnormality in one physiological system. Filiano and Kinney (1994) suggested that SIDS is likely due to an interaction of: 1) a developmental window of vulnerability; 2) intrinsic physiological differences in infants affecting each one's vulnerability; and 3) environmental factors. An infant's vulnerability may lie latent until the infant reaches a developmental window of vulnerability and is exposed to an external stressor. I think it is safe to say that most researchers at the Conference accepted this theoretical model. Thus, it is likely that an understanding of the etiology of SIDS will require a new paradigm for understanding human disease.

When one thinks of sudden death, one usually thinks of heart failure or respiratory failure. Some investigators have described genetic abnormalities of cardiac repolarization, which may predispose infants to the sudden development of fatal cardiac arrhythmias. These would not be able to be detected post-mortem. However, a large study in Italy, by Schwartz and colleagues, suggests that the prolonged QT interval syndrome may cause a number of SIDS deaths. We now know that several genetic mutations, which can be detected in post-mortem tissues by DNA testing, may have been present in some infants who have died. This

research indicates that these types of cardiac abnormalities can cause sudden death, which is indistinguishable from SIDS. However, it is unclear if these rare genetic disorders comprise a substantial proportion of SIDS. Since it is not known if these disorders are frequent, there is not

The Triple Risk Model of SIDS



enough evidence to suggest that infants should be routinely screened with ECGs to attempt to identify such abnormalities prior to death. There was actually not much discussion of this in Yokohama.

SIDS Pathology Researchers



Roger Byard
Australia



Henry Krous
California, USA



Torleiv Rognum
Norway



Martin Schlaud
Germany

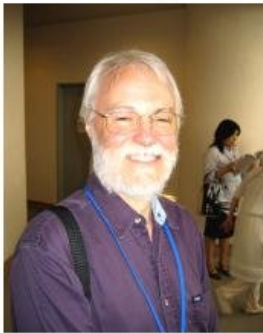
Another possibility is that SIDS may be due to a sudden respiratory arrest, or apnea (prolonged

breathing pause). This has been a popular hypothesis for many years, but more recently it has fallen from favor. There appears to be little evidence that an isolated apnea is the cause of SIDS. The use of home apnea-bradycardia monitors, which sound an alarm if an infant stops breathing for ≥ 20 -seconds or if the heart rate drops below set levels, has not resulted in a drop in the SIDS rate, and it is not currently recommended as a strategy to prevent SIDS. Nevertheless, there are significant cardiorespiratory interactions, which may explain SIDS deaths through perturbations of the autonomic nervous system.

SIDS Physiology Researchers



Aurore Cote, Canada



Peter Fleming, UK



Claude Gaultier, France



Ron Harper, USA



R. Horne, Australia



Carl Hunt, USA



Tom Keens, USA



S. Nakagawa, Japan

Most SIDS researchers believe that the origin of the cause of SIDS lies in dysfunction of the portions of the brain involved in “life support”. SIDS occurs during sleep. Sleep disrupts breathing, and this causes hypoxia, even in normal infants not destined to die from SIDS. The low oxygen

resulting from an apnea is probably not sufficient to directly cause an infant’s death. However, research from post-mortem examinations of SIDS victims finds abnormalities in certain parts of the brainstem, which are thought to be important in the control of breathing and/or protective mechanisms when breathing fails. This suggests that many SIDS victims had abnormalities in the way their brains responded to environmental stresses, such as high CO₂ or low oxygen. High CO₂ and low oxygen can result from a prolonged apnea.

Arousal (waking up) is an important defense against danger-signaling stimuli during sleep, and many SIDS researchers believe that that a failure to arouse in response to such stimuli may contribute to SIDS. Many of the papers describing new research in arousal were presented in the *Andre Kahn Memorial Symposium on Arousal*. A great deal of research has been done on a normal infant’s ability to arouse in response to a variety of stimuli, including respiratory stimuli. Horne and Walker, and Hamutcu, Ward, and Keens studied infants at 1, 3, and 6 months of age. Both research groups found that infants in the first month of life are better able to arouse in response to low oxygen than older infants. The decrease in this hypoxic arousal corresponds to the increased risk of SIDS at 2-4 months

of age. It is possible that this brainstem mediated hypoxic arousal response is lost with growth, as cortical development inhibits more “primitive” brainstem responses. The late Andre Kahn, and his colleagues, performed research sleep studies on thousands of infants in Europe, some of whom subsequently died from SIDS. Kato and Kahn found that those infants who subsequently died from SIDS had fewer spontaneous arousals during sleep, than infants who did not die. Further, SIDS victims had more subcortical arousals, detected by EEG criteria. However, these subcortical arousals failed to progress to cortical arousals, which would allow an infant to fully awaken and respond to a potentially dangerous situation. Franco and Kahn found that infants with some SIDS risk factors had impaired arousal responses to sound. More research is required in this area. Nevertheless, these results suggest that infants with impaired spontaneous or induced arousals from sleep may be more vulnerable to a SIDS death. Many scientists now believe that anything, which inhibits an infant’s ability to arouse from sleep, may increase the risk of SIDS.



**Rosemary Horne, Ronald M. Harper, Adrian Walker, and Tom Keens.
SIDS Researchers on Arousal and Brainstem Mechanisms of SIDS.**

SIDS occurs at a peak age of 2-4 months. This is an age when infants are undergoing rapid and tremendous changes in brain development, particularly in cardiorespiratory control. From an engineering point of view, a system in rapid transition is intrinsically unstable. Thus, when the neurologic system controlling breathing is undergoing rapid change, it is also more likely to malfunction, and serious apnea can occur. However, in the 1990’s, the Collaborative Home Infant Monitoring Evaluation (CHIME) Study did not find that prolonged apneas occur at the age when SIDS



Ronald M. Harper, Ph.D., and Thomas G. Keens, M.D.

is most common. Thus, apnea alone is not likely to be the mechanism of death in SIDS. SIDS is not as simple as an infant simply stopping breathing during sleep.

Neurologic control of respiration and of cardiac function is linked. We now know that the autonomic nervous system, the life-support part of the central nervous system, links cardiac and respiratory function. Breathing has a profound influence on function of the heart, including its rhythm and blood pressure. The details of this relationship are beginning to be elucidated, but they are not completely understood. Nevertheless, we know that aberrations in breathing can alter cardiac responses to environmental changes. For example, adults with obstructive sleep apnea syndrome (OSAS), a disorder

where there are repeated occlusions of the upper airway during sleep, have serious cardiac complications from their primary respiratory disorder, including high blood pressure, cardiac arrhythmias, and sudden death. Similarly, children with other abnormalities in respiratory control (such as congenital central hypoventilation syndrome), have abnormal cardiovascular responses to changes in breathing or in the environment. These are mediated by aberrations in the autonomic nervous system's coupling of cardiac and respiratory function. It is possible that respiratory abnormalities in infants may cause cardiovascular collapse through autonomic nervous system mechanisms, and this cardiovascular collapse may cause sudden death – SIDS.

SIDS Physiology Researchers



H. Nishida, Japan



C. Poets, Germany



Brad Thach, USA



H. Togari, Japan



A. Walker, Australia



D. Weese-Mayer, USA

Do respiratory problems cause cardiovascular collapse in all infants? Do infants need to have abnormalities in the brain in order to have these abnormal reactions? Can “normal” mechanisms transform the brain to have aberrant cardiac responses to respiratory perturbations? Imaging studies of the brain's response to hypoxia or hypercapnia, using functional magnetic resonance imaging (fMRI), show that many parts of the brain are involved in these neural responses to cardiac and respiratory control, not just the brainstem. In a spectacular presentation in Yokohama, Harper and colleagues showed that the cerebellum has an important role in neural control of cardiorespiratory function. Similarly, midbrain areas,

including areas in the limbic system, also participate in cardiorespiratory control. Thus, lesions or damage to many parts of the brain may affect autonomic function. Some of these areas may be more susceptible to damage from hypoxia than the brainstem, which was traditionally thought to be the anatomic site of cardiorespiratory control.

Hypoxia (low oxygen) may also play an important role in SIDS. The CHIME study showed that normal infants experience significant hypoxia in their own homes during sleep. The Purkinje fibers in the cerebellum are especially sensitive to hypoxic damage. In fact, pathologists often diagnose hypoxia at autopsy when they see damage to Purkinje fibers. These neurons modulate autonomic nervous system control of blood pressure and cardiovascular instability. If Purkinje fibers are damaged by hypoxia, the unchecked autonomic brain structures fire sporadically and erratically, causing highly varying cardiorespiratory function. Specifically, the cardiac response to respiratory perturbations, may be unpredictable and potentially dangerous. Thus, hypoxia can make an infant vulnerable to abnormal, exaggerated, and/or life-threatening cardiovascular responses to respiratory

stimuli. Removal of this cerebellar modulation of cardiorespiratory control can lead to physiologic crises, perhaps resulting in death. These studies suggest that SIDS may be due to a combination of a respiratory and a cardiac death, with the link being aberrant autonomic nervous system function.



Claude Gaultier, Tom Keens, and Debra Weese-Mayer

is not thought to be an inherited disorder. That is, there is no genetic mutation, which has been shown to cause SIDS, or even to be present in a large number of SIDS victims. However, most genes have minor variations in structure (alleles or polymorphisms), which do not cause abnormal gene function. However, these polymorphisms may be associated with slight quantitative variations in gene function. For example, promoter polymorphisms of the serotonin transporter gene affect the amount of serotonin, a neurotransmitter thought to be important in cardiorespiratory control, which is available for signaling between neurons. There are two polymorphisms, a short and a long form. The long form metabolizes serotonin more quickly, leaving less available for neurotransmitter function. Narita and Weese-Mayer and their colleagues have found that the long promoter polymorphism of the serotonin transporter gene was more common in babies who died from SIDS than in controls. The long promoter polymorphism of the serotonin transporter gene does not cause abnormal function of the gene, which would cause a disease. Rather it simply metabolizes more serotonin than the short promoter polymorphism of the serotonin transporter gene. Having less serotonin available as a neurotransmitter may make some infants less resilient to coping with environmental changes, or it may slightly alter physiologic protective

Metabolic disorders are inherited conditions, which decrease the body's ability to generate the energy necessary to sustain life from ingested food. There are thousands of metabolic disorders, but disorders of the β -oxidation of fatty acids are thought to be most relevant to SIDS. These disorders decrease the body's ability to make the energy, especially under conditions of fasting, fever, or other stresses. While some investigators believe that metabolic disorders may explain some SIDS deaths, the proportion of deaths so explained is not known, and most investigators believe it is a small proportion.

Genetic factors may explain the increased vulnerability for SIDS in some infants. SIDS



Shirley Tonkin, M.D., Australia. First suggested dangers of prone sleeping in 1972.

mechanisms, such that some infants might be more susceptible to environmental or other challenges. Similarly, Weese-Mayer found mutations or polymorphisms in other genes, though to be important in development of the autonomic nervous system, which were more common in SIDS victims than in controls. These studies do not prove that SIDS is a genetic disorder. However, such genetic variation may be a partial basis for why some infants are more vulnerable than others in Filiano and Kinney's triple risk model.



In summary, the cause of SIDS is not known. Investigations into the role of cardiac arrhythmias and metabolic disorders must continue. However, SIDS is generally not thought to be due to a single abnormality in a single physiologic system. SIDS is not thought to be due to an infection, environmental toxin, or nutritional deficiency. If there is a pre-existing abnormality in babies who die from SIDS, it must be subtle, as it has eluded identification by researchers for decades. It is more likely that small differences in infant vulnerabilities, such as might be caused by genetic polymorphisms, predisposing to autonomic nervous system instability, stimulated by an

environmental stressor, occurring in a developmental window of vulnerability, all come together to cause a SIDS death.

The Conference ended with a celebration that Back to Sleep public health activities have saved thousands of babies' lives around the world over the past two decades, and of the prospect of new advances by unification of SIDS organizations internationally.

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