

Sudden Infant Death Syndrome

TO THE EDITOR: Kinney and Thach (Aug. 20 issue)¹ review the putative terminal respiratory pathway associated with the sudden infant death syndrome (SIDS), and they indicate a life-threatening event and failure of arousal as the first steps in the respiratory pathway to SIDS. The authors mention only central cortical and subcortical structures involved in arousal mechanisms, without referring to peripheral arterial chemoreceptors as the carotid body, the role of which in arousal from asphyxial events is widely accepted. Prematurity and exposure to smoke also increase the risk of SIDS and adversely affect the response of the peripheral arterial chemoreceptors.^{2,3} These chemoreceptors undergo structural and functional development during the postnatal period, with a gradual increase in hypoxic sensitivity.^{3,4} Prematurity causes intrinsic abnormalities of the response of the peripheral arterial chemoreceptors, which may be further worsened by prematurity-associated intermittent hypoxic events or oxygen therapy. Intermittent hypoxia may cause hypersensitivity of the peripheral arterial chemoreceptors, which may increase the risk of SIDS, precipitating unstable respiration through apneic responses after sighs or brief arousals.²⁻⁴ Conversely, exposure to hyperoxia has been reported to cause hyposensitivity of the peripheral arterial chemoreceptors, possibly leading to an ineffective response. Perinatal exposure to nicotine also blunts the function of the peripheral arterial chemoreceptors through changes in expression of neurotransmitters and neuro-modulators.³⁻⁵

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TO THE EDITOR: In discussing the causes of SIDS, Kinney and Thach focus on aberrant arousal mechanisms in the brain, particularly in the medulla.

We have shown that the Ljungan virus is present in infants with SIDS.¹ This evidence extends beyond the small fraction of cases of SIDS that are associated with rare infectious agents and observations that incidental infections from well-known agents may also be present. In our work, the incidence of the syndrome in humans was correlated with the cyclic numbers of native rodent carriers of Ljungan virus in northern Sweden and the presence of the virus in several patients with SIDS and SIDS-related syndromes.¹ We also reported on a patient with Ljungan virus in the medulla oblongata itself.¹ Supporting data show that Ljungan virus is a factor in intrauterine fetal death² and in central nervous system malformations in humans³; furthermore, this suite of perinatal outcomes was mimicked in a mouse model of Ljungan virus disease.⁴ The data point to a new hypothesis of SIDS causation due to a novel infectious agent.

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Dr. Niklasson reports being a codirector of Apodemus and having several patents involving Ljungan virus. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: We have noted that in the United States, the excess risk of SIDS among boys is 50% (ratio of boys to girls, 3:2), not 100% (ratio of boys to girls, 2:1).^{1,2} Furthermore, an excess risk of SIDS among boys is not itself remarkable, because the rates of total deaths among infant boys in all disease categories except neoplasms, as listed in the *International Classification of Diseases* in the United States in the 1979–2005 period, were greater than the corresponding rates of deaths among infant girls.^{1,3} Rather, the consistent year-to-year 50% excess risk of SIDS among boys in the United States is remarkable because it implies a possible genetic recessive X-linked condition associated with a greater risk of SIDS among subsequent siblings of infants with SIDS.^{2,3}

Kinney and Thach suggest that such previous cases of SIDS involving the same caretaker (or recurrent life-threatening events in an infant with SIDS) may indicate the possibility of infanticide. Fortunately, this concept changed in the United Kingdom in 2003 after three high-profile criminal prosecutions occurred.⁴ At trial, an expert witness famously said the chances of two siblings dying of SIDS were “73 million to one.”⁵ This statement helped to convict all three mothers who were later cleared after this notorious statistic was cast into disrepute.

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THE AUTHORS REPLY: We agree with Porzionato et al. that peripheral, as well as central, deficits in systems mediating hypoxic responses are important to consider in SIDS, and that analysis of the carotid body in SIDS merits attention. Different types of analyses have been reported to date in the carotid body in cases of SIDS, with conflicting results.^{1,2}

We are aware of the study by Niklasson et al. concerning the potential role of the Ljungan virus in SIDS.³ We, however, do not find the evidence sufficiently compelling at present. The immunocytochemical study of virus expression in SIDS tissue sections was limited by a small sample size and a lack of controls (i.e., infants who died from known noninfectious causes). The photograph of viral expression in the article by Niklasson et al. shows, in our opinion, immunostaining in axonal fibers and not, as suggested, in neuronal-cell bodies, raising the possibility that this staining was nonspecific. A tissue control without the primary antibody was not shown for the reader's assessment of staining specificity.

Published studies of rates of SIDS and sex preponderance report different values, such that infant boys are 30 to 50% more likely than girls to be affected.⁴ In a study of the epidemiology of SIDS in Finland, the male-to-female ratio varied from 0.7 to 4.5, with a mean of 1.8.⁵ Thus, the sex ratio in SIDS varies according to different studies, including 2:1, as we cited in our article, and is not invariably 1:1.5, as cited by Mage et al. Their hypothesis of a possible genetic recessive X-linked condition associated with a greater risk of SIDS among subsequent siblings awaits confirmation. In this regard, one of us recently reported on a genetic mouse model of SIDS with male bias and a chromosome locus that was sex-specific.⁶ Fi-

nally, we thank Mage et al. for their thoughts about multiple deaths from SIDS in a family and the uncertain relationship of these deaths to infanticide. Infanticide, in our opinion, still remains in the differential diagnosis of more than one death from SIDS in a family.

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Since publication of their article, the authors report no further potential conflict of interest.

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Bacterial Pathogens and Death during the 1918 Influenza Pandemic

TO THE EDITOR: A review of recut lung-tissue specimens and published autopsy series from the 1918 influenza pandemic suggests that secondary bacterial pneumonia¹ was an important cause of death, consistent with our preliminary analysis of antemortem blood cultures and the time to death of the patients.² We review here studies that reported more than 10 sterile-site antemortem cultures from adults with pneumonia and those without pneumonia in an extensive archive of articles about the 1918 pandemic in any language (www3.niaid.nih.gov/topics/Flu/1918/bibliography.htm). Bacteria were recovered in only a few blood cultures for patients who had influenza but not pneumonia (mean among all the reports, <1%) but were more commonly isolated from cultures of samples from patients with influenza-associated pneumonia (mean, 16%; range, 2 to 50), particularly those who died (40%) (Table 1 and the Supplementary Appendix, available with the full text of this article at NEJM.org). Moreover, 80% of pleural-fluid and lung cultures from patients with pneumonia yielded bacteria (range, 57 to 100). The studies with lower reported rates of positive culture may have obtained cultures early, overdiagnosed pneumonia, or had problems culturing fastidious organisms. *Streptococcus pneumoniae* and hemolytic streptococci (probably *S. pyogenes*) comprised 71% and 28% of positive cultures (whether blood or pleural and lung), respectively; *Staphylococcus aureus* was less common among the cultures (1%).

The insensitivity of blood culture for identifying pneumococcal pneumonia (with detection in only approximately 3% and 20% of cultures from children and adults, respectively) as compared with the high percentage of positive lung cultures³ suggests that bacterial infections, especially pneumococcal infections, were a major cause of influenza-associated pneumonia and death among both military personnel and civilians in 1918–1919. The distribution of pneumococcal serotypes shifted toward less invasive serotypes during that period as compared with the pre-1918 period, suggesting that the 1918 influenza virus increased host susceptibility to less-invasive pneumococci.²

Children receiving pneumococcal conjugate vaccine in a double-blind, randomized trial had a 45% reduction in the rate of hospitalization for seasonal influenza-related pneumonia.⁴ Recent use of pneumococcal conjugate vaccine in developed countries, as well as the availability of antibiotics since the 1940s, influenza vaccination, use of antiviral agents, and reduced virulence of pandemic viruses, may all have reduced the mortality associated with influenza pandemics. Although viral pneumonitis alone has caused deaths, a recent report from the Centers for Disease Control and Prevention⁵ showed that 29% of the patients who died from infection with the 2009 pandemic influenza A (H1N1) virus had evidence of bacterial infection with pneumococci predominantly of types not present in the conjugate vaccine. The currently increased incidence of staph-