This Month In The JOURNAL of PEDIATRICS

August 2016 • Volume 175



## Blunted response: smoke, illicit substances, and how babies breathe

— Clyde J. Wright, MD

Despite our best efforts, rates of death due to sudden infant death syndrome (SIDS) remain unacceptably high. A litany of risk factors predisposing babies to SIDS has been identified, including maternal smoking and substance misuse. However, the mechanisms linking maternal smoking and substance misuse to SIDS are unknown. In this volume of *The Journal,* Ali et al demonstrate that during the time when the risk of dying from SIDS peaks (6-12 weeks of age), term infants born to mothers who smoke or misuse substances have a blunted ventilatory response to inhaled carbon dioxide when compared with controls. Specifically, control infants demonstrate an expected and reliable increase in mintue ventilation when challenged with either 2% or 4% carbon dioxide. In contrast, the change in minute ventilation in similarly exposed infants born to mothers who smoke or misuse substances was significantly less. It is attractive to hypothesize that infants exposed to smoke and other illicit substances—previously shown to carry a significant SIDS burden—are predisposed to complications arising from situations that require an intact venilatory response. These data provide important insights into the potential mechanisms linking prenatal exposures and SIDS. How will we use this information? What is behind the impaired response – and is it permanent? Can we modify this impaired response, especially during the period of highest risk of dying of SIDS? Should more babies be studied to confirm this association, or should we begin to cousel families based on this observation? While we work to answer these questions, it seems appropriate to emphasize that the families taking care of these babies must take great care when creating the sleep environment for these incredibly high-risk infants.

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## Is it better to overtreat or undertreat?

— Janet H. Silverstein, MD

Yogi Berra, an exceptionally gifted baseball player, was a font of wisdom. One of his most famous quotes, "When you come to a fork in the road, take it," applies to the conundrum tackled by Paone et al in this volume of *The Journal.* Approximately 43% of infants and 10% of older children with congenital hypothyroidism have elevated levels of both thyrotropin (TSH) and thyroxine (T4). When both T4 and triiodothyronine (T3) are elevated, pediatricians are in the untenable position of having to determine if they should overtreat in an attempt to normalize the TSH at the possible expense of increasing the T4 above normal, when studies have demonstrated impaired school performance, lower IQ, and a higher risk of attention deficit in children who had high T4 concentrations in infancy (*J Pediatr* 2000;136:292-7; *Pediatrics* 2003;112:923-30). Or, should they attempt to maintain normal T4 values while TSH concentrations remain mildly elevated? Although the evidence that low T4 levels during the time of rapid brain growth affects intellectual functioning, the evidence that elevated TSH values during the first 3 years of life is less robust, though one study reported poorer school performance in children who had TSH elevations in infancy (*Acta Paediatr* 2001;90:1249-56).

Due to the lack of data, we do not know which fork to take in this particular road. The cause of the abnormal lack of suppression of TSH with adequate levothyroxine administration is unknown. Affected infants might have abnormally low thyroid gland secretion of T3, abnormally low conversion of T4 to T3, or abnormal central feedback with lack of normal TSH suppression (ie, central resistance to thyroid hormone).

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Paone et al hypothesized that the lack of suppression of TSH by appropriate doses of levothyroxine (LT4) could be overcome with the addition of liothyroninie (LT3), as shown in other studies (*Horm Res Paediatr* 2010;73:108-14; *J Pediatr Endocrinol Metab* 2011;24:347-50). In order to assess this hypothesis, the authors performed a retrospective analysis of clinical data of 12 patients with CH with both high T4 and TSH values. Six of them had been treated with LT4 alone followed by LT4 + LT3 and 6 only received LT4. The addition of LT3 resulted in the normalization of TSH (mean 4.3 mIU/L, down from 10 mIU/L pre-T3 treatment , vs 8.5 mIU/L in the T4 monotherapy group). The T4 values were likewise normalized, with a mean decrease of 23% ± 9% from pretreatment values. T3 concentrations remained normal for age.

Because this was a retrospective study, the groups were neither matched for the age of treatment initiation nor given a neurodevelopmental assessment. However, this is a promising treatment for infants with persistent elevation of TSH and T4 despite appropriate treatment with levothyroxine. Long-term randomized controlled trials are needed to assess the effect of this regimen on thyroid hormone values. But, the real question that must be answered is not whether the laboratory values can be normalized but whether this regimen can improve neurocognitive functioning in these children, including not only intelligence but also school performance. And, hopefully, this study will help us to determine which fork in this particular road we should take.

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## Do we end life well?

— **Paul G. Fisher, MD**

Many general pediatricians and subspecialists believe that their clinical acumen caring for a child while ill extends equally well to the end of life. But do we end life well? Do we meet the needs of families and their dying child? In this volume of *The Journal,* Lövgren et al report their results from a cross-sectional survey of Swedish parents whose 40 children died from spinal muscular atrophy types I or II. Although end of life from this neurodegenerative disease may not exemplify all other pediatric deaths, and some practices in this study could be specific to Swedish culture, the findings regarding how we deliver care are only slightly reassuring and perhaps more heart wrenching. Among parents who talked with a physician about how they wanted their child to die, all but 2 of 26 had their wishes fulfilled. All those parents who wanted their child to pass away in the hospital had their request met, but 6 of 16 who wanted their child to die at home did not have their wish fulfilled. Siblings were almost always not engaged in the dying process. More than one-quarter of parents reported that health care staff did or said something stressful at the end of life.

These findings study should make us want to do better. As the investigators note, communication with the parents is paramount. We should not assume but rather explore parents' wishes, values, and spirituality. Cultural differences need to be appreciated. Our everyday clinical practices need to be altered and sometimes radically changed at the end of life. The actions of health care staff can be particularly lasting memories. As the authors note, especially supportive efforts from providers after death were dressing the child and making the room beautiful, collecting mementos, showing feelings openly, giving small gifts, and opening the window to release the soul.

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## Iron deficiency anemia: like mother, like child

— **William S. Ferguson, MD**

Iron deficiency remains a leading cause of anemia worldwide. The prevalence among infants and toddlers in the US remains close to 10% despite widespread adoption of iron-fortified formulas and the recommendation to delay the introduction of cow's milk until 1 year of age; in developing countries the frequency is often much higher. In addition to anemia, there is evidence that iron deficiency causes long-term neurocognitive deficits that can persist despite iron replacement therapy. Although the most recent US Preventive Services Task Force guidelines recommend iron supplements for high-risk infants (low birth weight or premature), there is a surprising paucity of