# Neonatal Hyperbilirubinemia and the Potential Risk of Subtle Neurological Dysfunction

**Commentary on the article by Soorani-Lunsing *et al.* on page 701**

VINOD K. BHUTANI

*Newborn Pediatrics, Pennsylvania Hospital, University of Pennsylvania Health System, 800 Spruce Street, Philadelphia, PA 19107*

Before the 1994 recommendations of the AAP for the US population (1), the pediatric literature was replete with articles on a kinder, gentler demedicalized management of neonatal hyperbilirubinemia because of the apparent "lack of evidence" of bilirubin neurotoxicity in term and apparently healthy babies (2–5). It was claimed that "most studies have failed to substantiate significant associations between a specific level of total serum bilirubin (TSB) during nonhemolytic hyperbilirubinemia in term newborns and subsequent IQ or serious neurologic abnormality (including hearing abnormality)" (1). The 1994 recommendations were implemented and placed in practice even though it was recognized by some that credible studies had detected subtle differences in outcome associated with TSB levels (6–9). In their article, Soorani-Lunsing *et al.* observe an association of increasing minor neurologic dysfunction throughout the first year of life (study limited to the first year) to the degree of hyperbilirubinemia (233 to 444 ìmol/L) that appears to have a dose-response relationship (10).

The probability of "subtle" or minor neurologic abnormalities in relation to hyperbilirubinemia is of prime clinical importance. At the very least the issue should be prioritized for research and either proven or disproven. The data presented by Soorani-Lunsing *et al.* (10), even with the limitations of the descriptive methodology, should be reviewed in the context of the historical data and the recent clinical experiences of bilirubin induced neurologic dysfunction (11).

In a Pilot Kernicterus registry, over 90 cases of Kernicterus have been compiled in term and near-term babies born in the US since 1984; most since 1990 (12). The number must be an underestimate of the actual number that have occurred in the entire country because there are no formal processes to document such cases (even though more cases continue to be reported to this registry). This recent reemergence of acute and chronic bilirubin encephalopathy has been attributed to a lack of concern about jaundice and the toxic potential of bilirubin (whether related to the marginal bilirubin excretory capacity in normal newborns or the enhanced bilirubin production) that has influenced clinical practice (11). Unfortunately, these attitudes of the 1990s are not limited to the US but seem to have spread across the Atlantic: recent report on series of 6 Kernicterus cases (from 1994 to 1998) from Denmark (13) along with earlier case reports from New Zealand (14) and Canada (15). Pediatricians who have managed babies with neonatal hyperbilirubinemia that progress to clinical signs of either acute or chronic bilirubin encephalopathy often feel stigmatized and are disinclined to discuss, review or publish their experience. Thus, the scope of the true incidences of overt kernicterus as well as possible "subtle" neurologic deficits cannot be ascertained without a formal investigational approach.

"Subtle" neurologic deficits have been poorly labeled and inadequately researched. The subtlety refers to the physical signs but not to the clinical and personal impact of the deficit. In the original analysis of the Collaborative Perinatal Project conducted in 1960s, minor deficits included as gait abnormalities, loss of fine motor coordination, awkwardness (5, 11) should be considered significant and potentially "serious" abnormalities. We as pediatricians need to be responsible for and hope to enhance academic and athletic abilities of our children; the data reported by Soorani-Lunsing *et al.* raises significant questions. These need to be addressed by deliberate, meticulous and scientific investigation.

Investigations of bilirubin induced neurologic dysfunction (BIND) to further elucidate mechanisms of target cellular injury (16) as well as assess clinical correlates of newborn neurologic abnormalities graded to incremental levels of bilirubin would allay the concerns of practicing pediatricians. A clinical BIND scoring of the newborn, as suggested by Johnson and Brown (17), and its correlation to TSB and the TSB/albumin ratio, to acute changes in brainstem auditory-evoked responses as well as to measures of unbound bilirubin and to rates of bilirubin production and elimination may provide objective and evidentiary bases for clinical management of a baby with significant hyperbilirubinemia. Another practical, safer and judicious approach would be to identify and track babies with "moderate" hyperbilirubinemia (as per Soorani-Lunsing *et al.*) or babies with TSB values above the 97th percentile track on the hour-specific bilirubin nomogram (18).

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# Melatonin: The Next Panacea?

## Commentary on the article by Gitto et al. on page 756

PHYLLIS A. DENNERY

*Department of Pediatrics, Stanford University School of Medicine, 750 Welch Rd. #315, Palo Alto, CA 94304-5731, U.S.A.*

Neonatal sepsis is a frequent occurrence in the nursery. The morbidity associated with this condition is still significant despite the availability of antibiotics (1). This is due to factors other than the mere presence of an organism. In sepsis, liver mitochondria can increase rates of hydrogen peroxide and hydroxyl radical production *via* alterations in complex II activity (2). Cytokine release and resultant transcriptional activation of various genes can also result in increased reactive oxygen species (3). Some reports indicate that septic neonates have altered antioxidant status and several investigators have demonstrated increased oxidative stress in septic adults (2, 4). Based on this premise, Gitto and colleagues (5) evaluated the protective effects of melatonin therapy in neonates with sepsis by measuring a marker of oxidative stress.

In this small study involving only 20 newborns with sepsis, melatonin dissolved in 1:90 ethanol was administered orally to neonates within 24 -48 h diagnosis. Melatonin treated infants were less often classified as septic and demonstrated a reduction in markers of lipid peroxidation [malondialdehyde and 4-hydroxynonenal (4-HNE)]. This study provides encouraging evidence for the use of melatonin as an adjunct therapy in the treatment of neonatal sepsis. However, this study population is small and the criteria used for defining sepsis did not necessarily require that a blood culture be positive. Although we do not always identify the bacterial organisms responsible for neonatal sepsis, the lack of absolute confirmation of sepsis raises concerns about the nature of the illness in these patients. Would the infants have improved even if they were not given melatonin? Additionally, a change in serum malondiadldehyde and 4-HNE in the first four hours of life is difficult to reconcile with a change in clinical status 24 to 48 h later. We are not told whether this change persists or whether this difference was only transient. In either case, the association of decreased oxidative markers and improved clinical status is not necessarily causative.

As neonatologists, we are unfortunately quick to espouse therapies that later prove to be ineffective or harmful. As with most compounds, melatonin has multiple actions including its effect on the pineal gland and the sleep/wake cycle (6). The radical scavenging effects of melatonin have been proven *in vitro* and in animal models (7, 8) but the need for oral administration can be limiting in some instances where intestinal absorption is limited. This is particularly common in sick neonates. Furthermore, the vehicle, ethanol, can have both positive and negative effects. We have heard many reports on the antioxidant effects of moderate alcohol intake (9–11). This could suggest that the antioxidant effect of the melatonin preparation was not due entirely to melatonin itself although ethanol was used at very dilute concentrations. In contrast, ethanol ingestion can also cause oxidative stress (12) but this may be less relevant at the concentrations used in this study. This question is not answered because the controls did not receive the vehicle alone.

Despite these concerns, this study shows promise because multiple parameters of infection were altered in association with melatonin administration. Nonetheless, before heralding the next panacea, one must proceed with extreme caution. At the risk of stating the obvious and unoriginal, a large multicenter, randomized, controlled trial needs to be conducted to confirm whether this beneficial effect will survive more rigorous scrutiny.

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