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CORRESPONDENCE

To the Editor: I have read with interest the provocative article by Soorani-Lunsing *et al*. (1), as well as the accompanying editorial and commentaries by experts in the field (2–5). The authors of this study report that moderate hyperbilirubinemia is associated with an increase in minor neurologic dysfunction (MND) with a "strong" dose-response relationship. In another publication by some of the same investigators, infants with MND were found to be at high risk for subsequent behavioral and learning problems at school age (6). Based on these findings the authors recommend lowering bilirubin levels before they get to the "danger zone" (≥335 μmol/L).

In his editorial, Ohlsson (2) raised several serious methodological concerns with ascertainment of the cohort, small sample size, subjective assessment measures, unblinded assessments, and most surprisingly, lack of bilirubin measurement in the control group. Together these preclude an unbiased answer to the study question. None of these limitations were addressed by the authors in their paper. In recommending a more aggressive approach to phototherapy to lower bilirubin levels, the authors cite a few minor side effects in the neonatal period. However, other investigators have shown that visual and auditory orientation responses in infants treated with phototherapy are compromised when phototherapy is terminated on day 4, and persist for as long as 1 month later (7). Poor ability to follow human face and voice may have the potential to impair early developmental interaction between the infant and the parents. Further, as Ohlsson (2) and Hintz and Stevenson (3) point out, the study period of 12 months is insufficient time to evaluate the ultimate impact of hyperbilirubinemia on later childhood outcomes. Unfortunately, follow-up of this particular cohort to an older age will not necessarily provide more definitive answers due to the biases alluded to earlier.

The three accompanying commentaries provide valuable insights into many important issues on the subject, despite the methodologic shortcomings of the original article. Maisels and Newman (4) rightly caution that before changing current practices, we need better evidence not only that the intervention is effective, but also that the benefits justify the risks and costs. At best, the article by Soorani-Lunsing *et al*. raises concerns which require further large-scale, well-designed prospective studies to determine whether infants are being harmed by what were previously considered "safe" levels of plasma bilirubin, and whether these effects are indeed long lasting. Given the substantive methodologic concerns, one cannot possibly conclude that a causal relationship exists between moderate hyperbilirubinemia and MND.

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References

1. Soorani-Lunsing I, Woltil HA, Hadders-Algra M 2001 Are moderate degrees of hyperbilirubinemia in healthy term neonates really safe for the brain? Pediatr Res 50:701–705.
2. Ohlsson A 2001 Neonatal jaundice: Continuing concern and need for research. Pediatr Res 50:674–675 (editorial)
3. Hintz SR, Stevenson DK 2001 Just when you thought it was safe. . .. Pediatr Res 50:676–677
4. Maisels MJ, Newman TB 2001 Bilirubin and neurological dysfunction – Do we need to change what we are doing? Pediatr Res 50:677–678
5. Bhutan VK 2001 Neonatal hyperbilirubinemia and the potential risk of subtle neurological dysfunction. Pediatr Res 50:679
6. Hadders-Algra M, Touwen BCL 2002 Perinatal events and soft neurological signs in neurobehavioral outcome. Dev Neuropsychol, in press
7. Paludetto R, Mansi G, Rinaldi P, DeCurtis M, Ciccimarra F 1983 The behavior of jaundiced infants treated with phototherapy. Early Hum Dev 8:259–267

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Response

To the Editor: We read with great interest the letter of Professor Saigal. She pointed to the shortcomings of our study (1). We fully agree that the design of the study was not perfect. Still, our study suggested that term infants with moderate hyperbilirubinemia (233–444 μmol/l) more often showed minor neurological dysfunction (MND) during the first year of life than non-jaundiced matched controls. The differences in neurological outcome between the groups persisted in multivariate analyses where factors such as birthweight, gestational age at birth, gender, mode of delivery, and social class were taken into account. Moreover, within the jaundiced group a dose-response relationship was found: at the age of 12 months the severity of MND was related to the degree of neonatal hyperbilirubinemia. The degree of hyperbilirubinemia, which was related to the duration of hyperbilirubinemia and to treatment with phototherapy, explained neurological outcome at 12 months better than the duration of hyperbilirubinemia or phototherapy.

The Editorial and the Comments, which accompanied the publication of our study, reflect that the subject of the treatment of moderate degrees of hyperbilirubinemia in term infants is far from settled. We are talking about a large group of infants. How can they be managed best? Do they really run an increased risk of MND throughout childhood? Is a potentially increased risk related to a specific degree of hyperbilirubinemia? In other words, can we determine a safety level, *i.e.* a bilirubin-level below which the risk for neurological morbidity is not increased? In case moderate degrees of hyperbilirubinemia really are related to an increase in neurological morbidity, can this prevented by specific treatment such as phototherapy? Adverse neurological sequelae of phototherapy, in contrast to short-term beneficial ones (2), never have been reported. The study of Paludetto *et al*. (3), mentioned by professor Saigal, does not allow for the conclusion that phototherapy negatively affects the neonate's neurological condi-