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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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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-

tion. Paludetto *et al*. concluded that the poorer neurological performance of the jaundiced infants ($n = 12$) at 1 month could be the result of the jaundice itself or the phototherapy.

In order to be able to answer the critical questions raised, further research on the effect and management of moderate degrees of hyperbilirubinemia in full-term infants is urgently needed.

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To the Editor: The review article ‘Antioxidants as Therapy in the Newborn: Some Words of Caution‘ by Jankov, Negus, and Tanswell (1) is both timely and thought provoking. The concept that debilitating sequelae of premature birth may be due to oxygen radical disease was first hypothesized by Saugstad in 1988 (2). This model, as a possible unifying paradigm, was attractive because so many debilitating diseases might be prevented by dealing with a single cause, the inability of the premature newborn to cope with oxygen. This hypothesis is even more attractive because the ‘treatment‘ may very well be the administration of compounds whose structure and metabolism is well known.

The strength of this review article is that it forces us to pause and consider what we are attempting to do with antioxidant therapy since, as the authors state, ‘it remains unknown which radicals mediate injury, which oxidation products have roles in disease, and which cellular components are most susceptible, in specific disease entities of the newborn‘. They point out the ‘good‘ side of free radicals in cell signaling and caution against potential deleterious side effects of antioxidant intervention.

It is here where I wish to present a different perspective. There have been multiple studies of single antioxidant interventions in the premature, albeit with mixed results. There may be a need to use mixtures of antioxidants or cocktails and in order to cover a variety of cells and subcellular compartments in order to treat the total system. An example is the use of vitamin C (water soluble antioxidant) and vitamin E (lipid soluble antioxidant) which together appear to interact at the cell membrane and function in ways that neither could do alone (3, 4). Indeed, as we have reported for the antioxidant properties of human milk, it may not be individual components at all but entire systems with unique properties of their own that provide protection (5).

In reference to the ‘good‘ side of free radicals, the authors eloquently describe that role. However, this perspective is more appropriate for the healthy normal infant not for the premature infant whose lungs and other organs are exposed to oxygen, itself a free radical, before development has provided the tools to cope. It is the imbalance of uncontrolled overexposure to oxygen and under development of the natural antioxidant defense that creates a new problem that we may be able to assist with exogenous antioxidant intervention. Analogies are the use of lung surfactant to ‘prop up‘ the immature lung in oxygen uptake and gas exchange.

With the advent of technology that has increased the survival rate of the premature, we have brought into existence a new subset of the human population who would normally not need to cope with oxygen (both too little and then too much), unprepared, with inadequate tools. To wait, as the authors suggest, to fully understand the ‘ROS or RNS involved, the site of injury, and the biologic molecule to be protected‘ before attempting antioxidant therapy is sensible but not practical. I believe there is enough evidence now to consider trials with antioxidants. In the area of birth defects, there has been a dramatic drop in neural tube defects across North America that has occurred since fortification of flour with folic acid. We still do not know if the neural tube doesn’t close, re-opens or even how folate performs at the molecular level. If we had waited to fortify until we completely understood the process, there would be many more children in wheelchairs right now.

We believe that early intervention with antioxidants may benefit the premature infant (6). We are in the process of designing an animal model study to test that hypothesis. We also have, in progress, a trial in enterally fed premature infants to boost glutathione reserves.

At some point after risk/benefit assessment, and a considered appraisal of available data, a leap of faith is required no different than the first time lung surfactant, dexamethasone, erythropoietin or antibiotics were used to improve outcome. Some worked, some didn’t, and none were free of side effects. This is how we progress, and indeed how we have arrived at present treatment modalities for the low birth weight infant.

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