control group in the neonatal period. However, the precise timing of the examination (sometime between 3 and 8 d) and whether any of the infants were under phototherapy at the time of examination is not reported. Masking of the individual performing neurologic assessments, although difficult in many situations, can be extremely important as well. In the present study, it could be argued that masking was almost impossible in the newborn period, but unfortunately, the examiner was reported to be "occasionally" aware of the group membership of the patients at the time of the 12-mo examination.

Nonetheless, the authors present potentially disturbing information. The follow-up study of these children, especially with respect to auditory processing, is extremely important, although the study period of 12 mo is certainly not sufficient time to evaluate the ultimate impact of hyperbilirubinemia on later learning in childhood. However, these investigators do echo the earlier observations of Newman and Klebanoff (4) and those of Grimmer and coworkers (5) that the presence of minor motor problems, such as mild hypotonia, awkwardness or nonspecific gait abnormalities at age 7 y, and a higher prevalence of choreiform dyskinesia at 5 to 15 y, should not be played down. In combination, the evidence suggests that moderate hyperbilirubinemia [233 to 444 μM (13.6 to −25.9 mg/dL)] may represent a measurable risk for development of minor neurologic dysfunction throughout the 1st year of life.

Furthermore, it is also worrisome that four of the five children with minor neurologic dysfunction type 2 received phototherapy. Thus, phototherapy may not guarantee protection against bilirubin toxicity when STB levels are high [>330 μM (19.6 mg/dL)] or when the duration of exposure is long. In addition, although this small study suggests that some infants with STB levels >340 μM (20 mg/dL) will escape without apparent neurologic consequence, this observation should not serve as reassurance to pediatricians about unsafe practice. There are no data to suggest that the relationship between STB levels and neurologic consequences is linear, yet there is the inclination to consider the risk of hyperbilirubinemia in this way.

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Bilirubin and Neurological Dysfunction—Do We Need To Change What We Are Doing?

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

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Soorani-Lunsing and coworkers prospectively evaluated 20 jaundiced infants whose total serum bilirubin (TSB) levels ranged from 233–444 μM/L (13.6–26 mg/dL) and compared them with a control group of 20 healthy, nonjaundiced infants matched for sex and gestation (1). All infants were ≥ 36 wk gestation. They examined the newborns between the ages of 3 and 8 d, at 3 mo (using a video recording), and at 12 mo for the presence of two types of minor neurologic dysfunction (MND). MND type I was defined as the "presence of hypotonia without significant reflex or postural deviancies"; type II MND refers to "minor abnormalities in muscle tone regulation in combination with significant postural and reflex dysfunction." At 1 y, 5/8 (63%) infants with bilirubin levels between 19.6–26 mg/dL (335–444 μM/L) had type II MND *versus* 0/20 control infants ($p < 0.001$). How do the results of this Dutch study compare with those of other studies and what we should do about them?

In a 4 year follow-up of 83 infants, Johnson and Boggs found abnormal neurologic examinations in 14/68 (21%) children whose indirect bilirubin TSB levels were ≥ 15 mg/dL (257 μM/L) *versus* 0/15 in those with TSB levels <15 mg/dL (2) (one tailed $p = 0.047$). Eleven of 14 had "minimal cerebral dysfunction" and 3 had other abnormal signs including fine and gross motor delay, athetoid movements and mild mental retardation. (It is not stated how many of the 3 infants had some or all of these findings.) In this study, however, 53% of the infants had hemolytic disease and 33% were premature and there is no mention of whether or not the follow-up evaluations were performed in a blinded fashion. In a more recent German study by Grimmer *et al.* (3) children at 7 y of age whose neonatal TSB levels had exceeded 20 mg/dL (342 μM/L), scored significantly worse on a scale designed to measure choreiform and athetoid movements (the choreiform dyskinesia scale). In that study 8/16 (50%) children in the hyperbilirubinemia group *versus* 3/18 (17%) in the control group had abnormal scores (data not found in the original paper but kindly provided by Dr. Grimmer).

In their analysis of 33,272 children at age 7 y in the Collaborative Perinatal Project (CPP), Newman and Klebanoff also found an increase in abnormal or suspicious neurologic signs as neonatal TSB levels increased from 10 mg/dL (171 μM/L) to more than 20 mg/dL (342 μM/L) (4). All infants weighed $\geq$ 2500g at birth and those with hemolytic disease were not excluded from the analysis. In that study, 22.4% of children with TSB levels $\geq$ 20 mg/dL had abnormal or suspicious neurologic signs *versus* 14.9% of those whose TSB levels were less than 10 mg/dL (171 μM/L) ($p < 0.001$).

What can we learn from comparing these studies? Sample sizes in both the Dutch and German studies are very small, but the effect sizes large. A small sample size leads to very wide confidence intervals—in the Dutch study the 95% confidence intervals around the odds ratio of 9.47 (for MND at one year) were 1.67–53.65. In the much larger CPP, the adjusted odds ratio for the trend in abnormal or suspicious neurologic findings associated with TSB levels increasing above 10 mg/dL was only 1.12 per 5 mg/dL (86 μM/L) TSB category and the confidence intervals were very narrow (1.06–1.20). The effect size in both the Dutch and German studies may be larger than that in the CPP because of more sensitive instruments, but the measurements are subjective and blinding was not rigorous. Although examiners for the CPP also were not blinded, in the CPP the TSB level was only one of a multitude of variables evaluated (post hoc) for a relationship with developmental outcome, making the lack of blinding less problematic. Notwithstanding the differences in these studies, the finding of a relationship between rising TSB levels and minor neurologic findings in several studies, adds credibility to the claim that the observed relationship may be causal.

What should pediatricians do with this information? We have only one randomized control trial to which we can look for help. In the collaborative phototherapy trial of the National Institutes of Child Health and Human Development (NICHD), newborns were randomly assigned to receive phototherapy at designated bilirubin levels or to a control group that received no phototherapy (5). In infants weighing more than 2500g at birth, phototherapy was administered if the TSB level reached 13 mg/dL (222 μM/L) in the first 96 h, and exchange transfusions were done if the TSB reached 20 mg/dL (342 μM/L). Because TSB levels in both the study and control groups declined after study entry, both groups had almost identical mean peak TSB levels of 15.7 $\pm$ 2.5 mg/dL (268 $\pm$ 43 μM/L) and 15.6 $\pm$ 2.5 mg/dL (267 $\pm$ 43 μM/L) respectively (a range of about 11–21 mg/dL [188–359 μM/L]), but phototherapy lowered the serum bilirubin level in the treatment group significantly faster than in the control group. At age 1 y, a blinded neurologic examination identified no infant in either group with abnormal movements (dyskinesia, dystonia, or clumsiness) and 1/121 infants in the phototherapy group was diagnosed with hypotonia. Clumsy, awkward or uncoordinated children were equally frequent in both treatment arms at the 6-y follow-up (11.1% *versus* 11.4%) (5). Although 50% of the infants in both the phototherapy and the control groups were considered to have a hemolytic cause for their hyperbilirubinemia, the frequency of identified neurologic problems both at 1 y and at 6 y was substantially less than the 42% incidence of type 1 MND in the Dutch study infants with similar TSB levels of 13.6–18.7 mg/dL (233–320 μM/L).

In their conclusion the authors of the current study suggest that TSB levels of 335 μM/L (19.6 mg/dL) "should be avoided." To achieve this we would need to be much more aggressive with our use of phototherapy, perhaps returning to treating all infants when their TSB levels exceeded 14–15 mg/dL (239–257 μM/L). Unfortunately, we have no evidence that phototherapy or any other intervention will produce the desired outcome. Furthermore, even if it were effective, it is uncertain whether the benefits would justify the risks and costs. In the CPP, suspicious or abnormal neurologic findings occurred in 15.13% of the entire population and in 14.85% of those with TSB levels less than 10 mg/dL (171 μM/L). Thus if the TSB level in every infant in that population had been prevented from exceeding 10 mg/dL, the prevalence of abnormal or suspicious neurologic examination results at age 7 would decline only from 15.13% to 14.84% (4).

There is certainly good reason to want to prevent neurologic dysfunction, but before we embark on a radical change in our current approach to the management of the jaundiced newborn, we need better evidence that the intervention will improve the outcome and, most important, that the proposed intervention does more good than harm.

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