

ORIGINAL ARTICLE

Outcomes among Newborns with Total Serum Bilirubin Levels of 25 mg per Deciliter or More

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ABSTRACT

BACKGROUND

The neurodevelopmental risks associated with high total serum bilirubin levels in newborns are not well defined.

METHODS

We identified 140 infants with neonatal total serum bilirubin levels of at least 25 mg per deciliter (428 μmol per liter) and 419 randomly selected controls from a cohort of 106,627 term and near-term infants born from 1995 through 1998 in Kaiser Permanente hospitals in northern California. Data on outcomes were obtained from electronic records, interviews, responses to questionnaires, and neurodevelopmental evaluations that had been performed in a blinded fashion.

RESULTS

Peak bilirubin levels were between 25 and 29.9 mg per deciliter (511 μmol per liter) in 130 of the newborns with hyperbilirubinemia and 30 mg per deciliter (513 μmol per liter) or more in 10 newborns; treatment involved phototherapy in 136 cases and exchange transfusion in 5. Follow-up data to the age of at least two years were available for 132 of 140 children with a history of hyperbilirubinemia (94 percent) and 372 of 419 controls (89 percent) and included formal evaluation at a mean (\pm SD) age of 5.1 ± 0.12 years for 82 children (59 percent) and 168 children (40 percent), respectively. There were no cases of kernicterus. Neither crude nor adjusted scores on cognitive tests differed significantly between the two groups; on most tests, 95 percent confidence intervals excluded a 3-point (0.2 SD) decrease in adjusted scores in the hyperbilirubinemia group. There was no significant difference between groups in the proportion of children with abnormal neurologic findings on physical examination or with documented diagnoses of neurologic abnormalities. Fourteen of the children with hyperbilirubinemia (17 percent) had "questionable" or abnormal findings on neurologic examination, as compared with 48 controls (29 percent; $P=0.05$; adjusted odds ratio, 0.47; 95 percent confidence interval, 0.23 to 0.98; $P=0.04$). The frequencies of parental concern and reported behavioral problems also were not significantly different between the two groups. Within the hyperbilirubinemia group, those with positive direct antiglobulin tests had lower scores on cognitive testing but not more neurologic or behavioral problems.

CONCLUSIONS

When treated with phototherapy or exchange transfusion, total serum bilirubin levels in the range included in this study were not associated with adverse neurodevelopmental outcomes in infants born at or near term.

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N Engl J Med 2006;354:1889-900.

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IN OTHERWISE HEALTHY INFANTS, EXTREMELY high total serum bilirubin levels, usually more than 30 mg per deciliter (513 μ mol per liter), are known to cause kernicterus, but the risks associated with less extreme elevations of total serum bilirubin levels are unclear.¹ Treatment recommendations reflect this uncertainty. For example, the American Academy of Pediatrics recommends performing exchange transfusion for full-term, healthy newborns at least four days of age if their total serum bilirubin level is 25 mg per deciliter (428 μ mol per liter) or more and does not decrease sufficiently with phototherapy alone,² whereas a guideline included in a recent neonatology textbook³ recommends exchange transfusion for healthy full-term newborns who have total serum bilirubin levels of 20 to 25 mg per deciliter (342 to 428 μ mol per liter).

Previous studies addressing the sequelae associated with hyperbilirubinemia in full-term and near-term newborns have yielded mixed results and had several limitations.^{1,4-13} Because total serum bilirubin levels of 25 mg per deciliter or more are rare, most studies have included few subjects with levels that high. Many studies have included infants or young children, who might outgrow any subtle abnormalities identified. Some studies of older children (up to 13 years of age) have had high rates (80 percent) of loss to follow-up.^{11,12} Few have involved outcome assessments that were performed in a blinded fashion,^{11,13} that included examinations by child neurologists,^{11,12} or that addressed children's behavior or age-appropriate motor activities.¹³ None have followed large numbers of infants with extreme hyperbilirubinemia who were born in community hospitals. We designed our study to compare neurodevelopmental outcomes among infants with total serum bilirubin levels of 25 mg per deciliter or more with those among randomly selected controls. We used a cohort of infants from the Northern California Kaiser Permanente Medical Care Program^{14,15} who were born during a period when treatment of hyperbilirubinemia varied.¹⁶

METHODS

SUBJECTS

We conducted a prospective study that includes two of three cohorts in the Jaundice and Infant Feeding (JI_{Fee}) study, a follow-up study of infants with severe neonatal jaundice or dehydra-

tion and randomly selected controls. Those born from 1995 through 1996 had been identified in previous nested case-control studies.^{15,17} Study subjects were drawn from 106,627 live births at the Kaiser Permanente Medical Care Program from 1995 through 1998 and had a birth weight of at least 2000 g and a gestational age of at least 36 weeks (if born from 1995 through 1996) or at least 34 weeks (if born from 1997 through 1998). Eligible subjects had total serum bilirubin levels of 25 mg per deciliter or more within 30 days after birth (the case subjects) or were randomly selected (the controls) from the birth cohorts of 1995 through 1996 and 1997 through 1998 in a 1:1 ratio of projected subjects with dehydration or hyperbilirubinemia to controls (Fig. 1). We excluded 2 children who had died (1 in the hyperbilirubinemia group who died of sudden infant death syndrome without kernicterus and 1 control who died of apparent sudden infant death syndrome), 1 control whose primary care provider declined contact because the child's father had terminal cancer, and a total of 13 with genetic or congenital disorders liable to affect neurologic development. Institutional review boards of the University of California, San Francisco, the Kaiser Permanente Medical Care Program, and the State of California approved the study, and parents or guardians provided written informed consent for formal evaluations.

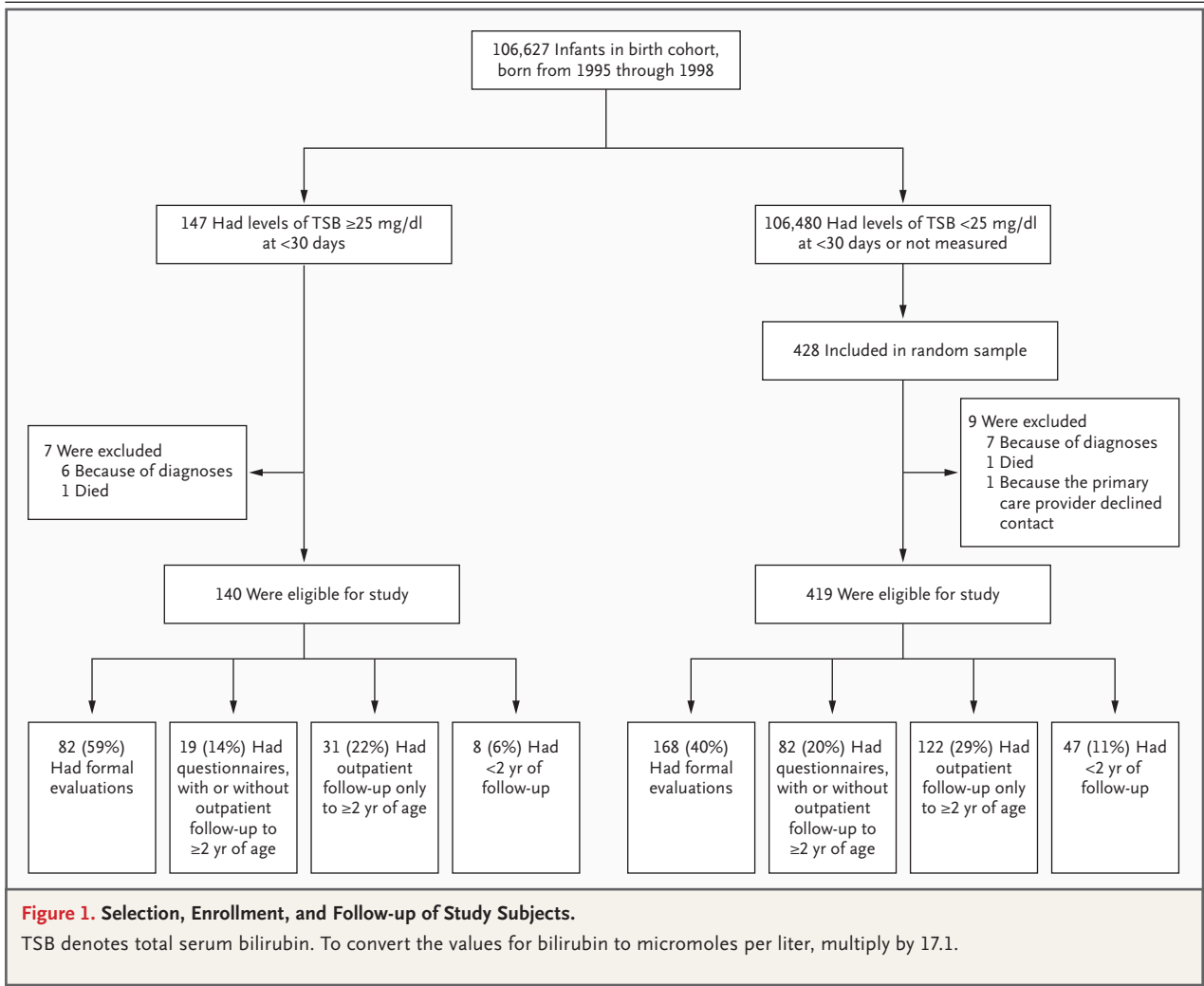
PREDICTOR VARIABLES

We obtained perinatal data on eligible subjects from the paper and electronic medical records of mothers and infants^{15,17} and additional data on potential confounding variables from caregivers, including assessments of parental depression¹⁸ (for which the Center for Epidemiologic Studies Depression Scale¹⁹ was used). We used data from birth certificates to categorize parents' race and level of education (linked for 99 percent of subjects) when these variables were missing from questionnaires. We used 2000 U.S. Census data on median household income in Census tracts (linked for 94 percent).

OUTCOME VARIABLES

Overview

Formal evaluations of neurologic development were performed, at a mean (\pm SD) age of 5.1 \pm 0.12 years, by examiners who were unaware of the subjects' study-group status. Parents who declined to



have formal evaluations performed were provided with a questionnaire-only study option. We also searched electronic records of the Kaiser Permanente Medical Care Program for codes for neurologic diagnoses, as recorded by treating clinicians, from the *International Classification of Diseases, 9th Revision*. These included codes 320 to 360 (nervous system disorders), 378 to 378.9 (strabismus), 389.1 and 389.2 (hearing loss), 773.4 and 774.7 (kernicterus), 780.5 (sleep disturbance), 781, 781.2, 781.3, and 781.9 (problems with movement, gait, coordination, or posture), 794 to 794.19 (abnormal brain imaging), and 796.1 (abnormal reflexes).

Neurodevelopmental Evaluations

Licensed child psychologists administered the Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI-R)²⁰ and the Beery–Buk-

tenica Developmental Test of Visual-Motor Integration, 4th edition (VMI-4).²¹ Child neurologists and a clinical nurse specialist in child neurology (who examined three subjects) conducted standard neurologic examinations and gave their overall impression using a five-point scale, with 1 point indicating a normal result, 2 points normal or questionable results, 3 points abnormal results with minimal functional disability, 4 points abnormal results with moderate functional disability, and 5 points abnormal results with severe functional disability. To maximize the sensitivity of the test, neurologists were instructed to select the category “normal or questionable” for anything that was slightly suspicious on examination. Research assistants assessed motor skills with the use of a motor-performance checklist, a validated 12-item screening instrument that includes items such as

catching a ball and cutting out a square and that assigns each item a score of pass (0) or fail (1).²²

Questionnaires

Parents completed the Parent Evaluation of Developmental Status (PEDS) questionnaire²³ and the Child Behavior Checklist (CBCL)²⁴ questionnaire, as part of participation in either the formal-evaluation group or the questionnaire-only group of the study (Fig. 1). The PEDS questionnaire is a 10-item instrument that queries parents regarding concern about areas of their child's development; possible answers are "no," "yes," and "a little." The CBCL is a checklist of 120 behavioral problems that are grouped into syndrome scales. The score for "internalizing" summarizes syndrome scales for "withdrawn," "somatic complaints," and "anxious/depressed," and the score for "externalizing" summarizes syndrome scales for "delinquent behavior" and "aggressive behavior."

STATISTICAL ANALYSIS

Bivariate associations were assessed with the use of the chi-square test, Fisher's exact test, the rank-sum test, or Student's t-test; only two-tailed P values are reported. To test for interactions between study group and participation in the study, we included interaction terms in either linear or logistic-regression models.

For multivariate analyses of outcome, we used backward stepwise multiple-regression analysis, with P values to remove 0.10 or more and a total serum bilirubin level of 25 mg per deciliter or more forced into all models. Additional candidate predictor variables included family income, parents' races and educational levels, maternal age, maternal smoking status, sex, gestational age, small size for gestational age (below the 10th percentile), five-minute Apgar score, initial exclusive breast-feeding, parental depression, and examining clinician; we imputed missing values for income for the multivariate analyses for nine subjects. The covariates included in each model are given in the Supplementary Appendix, available with the full text of this article at www.nejm.org. In addition to summary scores on each of the main instruments, we looked for differences in intelligence on each of the subtests in the WPPSI-R and for each item in the motor-performance checklist and the PEDS and CBCL questionnaires.

To address the possibility that the results of the neurologic examination might be biased be-

cause of preferential participation by control subjects whose parents were concerned about their child's development, we repeated the analyses of neurologic examinations, assuming that all unexamined children in the control group had normal results on the examination.

We hypothesized that some patients in the following subgroups of the hyperbilirubinemia group might be at increased risk for adverse outcomes: those with total serum bilirubin levels of at least 27 mg per deciliter (462 μ mol per liter) or at least 30 mg per deciliter, those with positive or trace positive direct antiglobulin tests or glucose-6-phosphate dehydrogenase (G6PD) deficiency, and those with a longer duration of hyperbilirubinemia on the basis of the estimated time from the first measurement of a total serum bilirubin level of 25 mg per deciliter or more until the level was below 20 mg per deciliter.²⁵ We examined each variable as a predictor of each of the main outcomes within the hyperbilirubinemia group, controlling (when the sample size was adequate) for confounding variables identified in the analyses between groups. In addition, we looked for an interaction between hyperbilirubinemia and gestational age, dichotomized at 38 weeks or more. All analyses were performed with the use of Stata software, version 8.2 (Stata).

RESULTS

ELIGIBILITY AND ENROLLMENT

A formal evaluation, completed parental questionnaire, or record of an outpatient visit at the age of two or more years was available for 94 percent of the subjects in the hyperbilirubinemia group and 89 percent of those in the control group (Fig. 1) ($P=0.06$). Parents or guardians of children in the hyperbilirubinemia group were more likely than those of children in the control group to give consent for a formal evaluation (59 percent vs. 40 percent, $P<0.001$). Total serum bilirubin levels were measured in about 26 percent of the children in the control group; in 10 percent, the level was at least 15 mg per deciliter (256 μ mol per liter), and in 2 percent it ranged from 20 mg per deciliter to less than 22.8 mg per deciliter (390 μ mol per liter). Children in the control group with total serum bilirubin levels of 15 mg per deciliter or more were more likely to undergo formal evaluations than those in whom total serum bilirubin levels either were not measured or were below 15 mg per deci-

Table 1. Demographic Characteristics of the Subjects and Their Parents, According to the Presence or Absence of Formal Evaluations.*

| Characteristic | No Formal Evaluation | | Formal Evaluation | | P Value for Interaction |
|--|-------------------------|-----------------------------------|-------------------------|-----------------------------------|-------------------------|
| | Control Group (N = 251) | Hyperbilirubinemia Group (N = 58) | Control Group (N = 168) | Hyperbilirubinemia Group (N = 82) | |
| Gestational age, <38 wk (%) | 10 | 36 | 14 | 37 | <0.001 |
| Documented TSB level of ≥15 mg/dl (%) | 7 | 100 | 14 | 100 | |
| Maternal age, ≥25 yr (%) | 72 | 90 | 74 | 83 | 0.004 |
| Exclusive breast-feeding at initial discharge (%) | 58 | 83 | 64 | 90 | <0.001 |
| Breast-fed for ≥6 mo (%)† | 50 | 67 | 45 | 41 | 0.24 |
| Mother's race or ethnic group (%)‡ | | | | | 0.05 |
| White | 42 | 29 | 46 | 48 | 0.08 |
| Black | 12 | 3 | 11 | 9 | 0.06 |
| Asian | 24 | 40 | 16 | 30 | 0.02 |
| Hispanic | 19 | 24 | 23 | 10 | 0.35 |
| Other or missing | 4 | 3 | 4 | 4 | 0.96 |
| Parents, any college (%)§ | | | | | 0.85 |
| Mother | 61 | 66 | 86 | 83 | 0.56 |
| Father | 59 | 60 | 74 | 75 | 0.89 |
| Median household income for U.S. Census tract of residence (\$)¶ | 57,349 | 61,739 | 62,073 | 60,150 | 0.06 |
| Median age of child at last recorded outpatient visit (yr) | 5.5 | 6.0 | 6.0 | 5.8 | 0.12 |
| Follow-up to age ≥2 yr (%)** | 81 | 86 | 100 | 100 | 0.38 |

* Hyperbilirubinemia was defined as total serum bilirubin (TSB) levels of 25 mg per deciliter or more. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

† Data on the duration of breast-feeding are from parents' responses to a questionnaire and were available for only 68 control subjects and 15 subjects in the hyperbilirubinemia group who did not undergo formal evaluation.

‡ Race or ethnic group was self-reported by the mothers at the time of admission for delivery. P values for race or ethnic group are for the overall chi-square test, and P values for each category of race or ethnic group are for the comparison of each race or ethnic group with the other groups.

§ Data are from birth certificates for subjects whose parents did not complete the questionnaires.

¶ Data on household income are from the 2000 U.S. Census.

|| P value was calculated by the rank-sum test.

** Follow-up data were obtained from outpatient visits, physical examinations, or parents' responses to questionnaires.

Table 2. Clinical Data on Subjects in the Hyperbilirubinemia Group, According to the Presence or Absence of Formal Evaluations.*

| Variable | No Formal Evaluation (N=58) | Formal Evaluation (N=82) | P Value |
|--|--------------------------------|-----------------------------|---------|
| Gestational age | | | 0.36 |
| <36 wk — no. (%) | 5 (9) | 3 (4) | |
| 36–37 wk — no. (%) | 16 (28) | 27 (33) | |
| ≥38 wk — no. (%) | 37 (64) | 52 (63) | |
| Mean — wk | 38.25 | 38.5 | |
| Maximal TSB — no. (%) | | | 0.73 |
| 25.0–26.9 mg/dl | 38 (66) | 52 (63) | |
| 27.0–29.9 mg/dl | 15 (26) | 25 (30) | |
| ≥30.0 mg/dl | 5 (9) | 5 (6) | |
| Age at maximal TSB — no. (%) | | | 0.88 |
| <3 days | 8 (14) | 4 (5) | |
| 3 to <5 days | 33 (57) | 53 (65) | |
| 5 to <7 days | 13 (22) | 16 (20) | |
| ≥7 days | 4 (7) | 9 (11) | |
| Estimated time from peak TSB to TSB< 20 mg/dl — no. (%) | | | 0.91 |
| <12.0 hr | 14 (24) | 17 (21) | |
| 12.0–23.9 hr | 17 (29) | 37 (45) | |
| ≥24.0 hr | 23 (40) | 26 (32) | |
| Data missing | 4 (7) | 2 (2) | |
| Estimated time from peak TSB to TSB< 25 mg/dl — no. (%) | | | 0.94 |
| <6.0 hr | 41 (71) | 59 (72) | |
| 6.0–11.9 hr | 9 (16) | 18 (22) | |
| ≥12.0 hr | 5 (9) | 5 (6) | |

liter (56 percent vs. 38 percent, $P=0.03$). Clinical and demographic characteristics of those with and those without formal evaluations were otherwise similar in the two groups (Table 1), except that in the hyperbilirubinemia group Hispanic subjects were underrepresented among those for whom formal evaluations were available ($P=0.02$ for interaction). The median Census-tract income was slightly higher among families of those in the control group for whom formal evaluations were available and lower among families of those in the hyperbilirubinemia group for whom formal evaluations were available ($P=0.03$ for interaction).

As compared with the control group, the hyperbilirubinemia group had a greater proportion of subjects who were born before 38 weeks of gestation, who were Asian, or who were exclusively breast-fed during the birth hospitalization. The

duration of breast-feeding, level of parental education, and income level did not differ significantly between the two groups.

CLINICAL CHARACTERISTICS OF THE HYPERBILIRUBINEMIA GROUP

Clinical characteristics of the children in the hyperbilirubinemia group are summarized in Table 2. The total serum bilirubin levels in these children were mostly below 27 mg per deciliter; only 10 subjects had levels above 30 mg per deciliter, with the highest level being 45.5 mg per deciliter (778 μmol per liter).²⁵ In most children, the total serum bilirubin levels peaked at three to seven days of age and were estimated to decline to below 20 mg per deciliter in less than 24 hours. The vast majority (93 to 94 percent) of the first total serum bilirubin levels of 25 mg per deciliter or

Table 2. (Continued.)

| Variable | No Formal Evaluation (N = 58) | Formal Evaluation (N = 82) | P Value |
|---|----------------------------------|-------------------------------|---------|
| Site of 1st measurement of TSB of ≥ 25 mg/dl — no. (%) | | | 0.85† |
| Birth hospital | 4 (7) | 5 (6) | |
| Outpatient visit | 54 (93) | 77 (94) | |
| Result of direct antiglobulin test — no. (%) | | | 0.84 |
| Negative | 43 (74) | 61 (74) | |
| Trace positive | 3 (5) | 1 (1) | |
| Positive | 3 (5) | 8 (10) | |
| Not tested | 9 (16) | 12 (15) | |
| G6PD activity — no. (%) | | | 0.49 |
| <7 U/g of hemoglobin (deficiency) | 1 (2) | 3 (4) | |
| ≥ 10 U/g of hemoglobin (normal) | 7 (12) | 4 (5) | |
| Not tested | 50 (86) | 75 (91) | |
| Treatment — no. (%) | | | 0.64† |
| Phototherapy alone | 53 (91) | 78 (95) | |
| Phototherapy and exchange transfusion | 3 (5) | 2 (2) | |
| Observation, follow-up, or both | 2 (3) | 2 (2) | |

* TSB denotes total serum bilirubin, and G6PD glucose-6-phosphate dehydrogenase. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. P values were calculated by the rank-sum test, unless otherwise noted.

† The P value was calculated by the chi-square test.

more were obtained in newborns who were outpatients. Direct antiglobulin tests were performed in 119 newborns (85 percent) and were positive in 15, all of whom had mothers with blood group O+. Of the 15 newborns who were tested for G6PD deficiency, 4 had a deficiency. All but four of the newborns with hyperbilirubinemia received phototherapy, and those four had peak total serum bilirubin levels of 25.2 mg per deciliter (431 μ mol per liter) or less that were documented as having declined spontaneously. Only five newborns received exchange transfusions, and of these, four had peak total serum bilirubin levels greater than 30 mg per deciliter and one had a level of 25.2 mg per deciliter at the age of 21.5 hours.

OUTCOMES

There were no significant differences between the hyperbilirubinemia group and the control group in the results of intelligence testing (according to the WPPSI-R) or visual-motor integration (according to the VMI-4) (Table 3). The results were unchanged when control subjects with total serum bilirubin levels of at least 10 mg per deciliter (171 μ mol per liter) were removed from the analysis.

Scores on neurologic examination of 2 (“normal or questionable”) or worse were documented in 17 percent of the hyperbilirubinemia group, as compared with 29 percent of the control group ($P=0.05$) (Table 4) (multivariate adjusted odds ratio, 0.47; 95 percent confidence interval, 0.23 to 0.98; $P=0.04$). Only 3 children in the hyperbilirubinemia group (4 percent) and 12 in the control group (7 percent) had scores of 3 (abnormal with minimal disability) or worse; the difference between the scores was not significant according to bivariate or multivariate analyses. Only two subjects (both in the control group) had abnormal examinations with moderate disability.²⁶ None of the control newborns had kernicterus or abnormal examinations with severe disability. Even assuming that all 251 children in the control group for whom no formal evaluations were available had normal results there would still be no significant increase in the risk of abnormal or questionable results in the hyperbilirubinemia group (relative risk, 1.5; 95 percent confidence interval, 0.87 to 2.6). There were no significant differences between the two groups according to the motor-performance checklist in mean total

Table 3. Results of Testing with the Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI-R) Test and the Beery–Buktenica Developmental Test of Visual–Motor Integration, 4th edition (VMI-4).

| Test | Control Group | Hyperbilirubinemia Group | Adjusted Difference (95% CI)* | P Value |
|--------------------------|---------------|--------------------------|-------------------------------|---------|
| WPPSI-R† | | | | |
| Verbal IQ | | | | 0.18 |
| No. of subjects | 162 | 81 | | |
| Mean score | 101.1 | 103.5 | 2.5 (–1.1 to 6.1) | |
| Performance IQ | | | | 0.29 |
| No. of subjects | 165 | 81 | | |
| Mean score | 106.0 | 107.0 | 0.5 (–2.9 to 4.0) | |
| Full-scale IQ | | | | 0.42 |
| No. of subjects | 162 | 81 | | |
| Mean score | 104.0 | 105.9 | 1.4 (–2.1 to 5.0) | |
| VMI-4‡ | | | | |
| Visual–motor integration | | | | 0.74 |
| No. of subjects | 165 | 81 | | |
| Mean score | 102.1 | 103.3 | 0.6 (–2.8 to 3.9) | |
| Visual perception | | | | 0.60 |
| No. of subjects | 164 | 80 | | |
| Mean score | 105.9 | 107.5 | 1.2 (–3.5 to 6.0) | |
| Motor coordination | | | | 0.54 |
| No. of subjects | 165 | 81 | | |
| Mean score | 100.4 | 101.3 | –1.3 (–5.6 to 2.9) | |

* Adjusted differences were calculated with the use of multiple linear regression analysis. The models varied, but most models included paternal race or ethnic group and level of education. The covariates included in each model are given in the Supplementary Appendix, available with the full text of this article at www.nejm.org. CI denotes confidence interval.

† Scores on the WPPSI-R test are distributed with a mean of 100 and an SD of 15. Scores in this study ranged from 46 to 149.

‡ Scores on the VMI-4 are distributed with a mean of 100 and an SD of 15. Scores in this study ranged from 45 to 150.

score, proportion of those with scores of 4 or greater or 5 or greater, or the proportion of those with a score indicating failure for any individual item on the checklist (Table 4).

Parents of children in the hyperbilirubinemia and comparison groups reported similar levels of concern in responses to the PEDS questionnaire (Table 4). Responses to the CBCL also showed no significant differences between the two groups in any of the eight syndrome scales or in total scores for the categories of internalizing or externalizing behaviors (Table 4). Of the 120 specific characteristics and behaviors, two (“impulsiveness” and “sleep problems”) were reported significantly more commonly in the hyperbilirubinemia group and two (“gets in fights” and “strange behavior”) were reported significantly less commonly in this group.

Records of one or more outpatient visits at the age of two years or older were available for 123 subjects in the hyperbilirubinemia group (88 percent) and 349 in the control group (83 percent); the median age at the last visit was 5.8 years and 5.7 years, respectively ($P=0.29$). Five subjects in the hyperbilirubinemia group (3.5 percent) received one or more neurologic diagnoses (migraine headaches, mixed hearing loss, and various eye-movement disorders), as compared with 18 in the control group (4.3 percent, $P=0.71$). The child who received a diagnosis of mixed hearing loss had normal hearing after tympanostomy-tube placement was performed.

In the hyperbilirubinemia group, neither the degree nor the duration of hyperbilirubinemia had a significant effect on outcomes, and there was no interaction with gestational age (data not

Table 4. Outcomes According to Neurologic Examination, Motor-Performance Checklist, Parent Evaluation of Developmental Status (PEDS) Questionnaire, and Child Behavior Checklist (CBCL).*

| Outcome | Control Group no./total no. (%) | Hyperbilirubinemia Group no./total no. (%) | Adjusted Odds Ratio (95% CI) | P Value |
|---|------------------------------------|--|---------------------------------|---------|
| Neurologic examination | | | | |
| Normal | 120/168 (71) | 67/81 (83) | | |
| Normal or questionable | 36/168 (21) | 11/81 (14) | | |
| Abnormal with minimal disability | 10/168 (6) | 3/81 (4) | | |
| Abnormal with moderate disability | 2/168 (1) | 0 | | |
| Abnormal with severe disability | 0 | 0 | | |
| Normal or questionable, or worse | 48/168 (29) | 14/81 (17) | 0.47 (0.23–0.98) | 0.04 |
| Abnormal with minimal disability, or worse | 12/168 (7) | 3/81 (4) | 0.50 (0.14–1.83) | 0.29 |
| Motor-performance checklist | | | | |
| Score, ≥ 5 [†] | 58/165 (35) | 30/81 (37) | 0.99 (0.54–1.82) | 0.98 |
| PEDS questionnaire | | | | |
| At least 1 answer of “yes” [‡] | 56/239 (23) | 26/96 (27) | 1.2 (0.67–2.10) | 0.56 |
| CBCL preclinical or clinical total score [§] | | | | |
| Internalizing behavior | 24/227 (11) | 9/95 (10) | 0.75 (0.32–1.79) | 0.52 |
| Externalizing behavior | 24/227 (11) | 13/95 (14) | 1.3 (0.60–2.63) | 0.54 |
| Outpatient follow-up to age of ≥ 2 yr | 349/419 (83) | 123/140 (88) | 1.13 (0.62–2.05) | 0.68 |
| ≥ 1 Neurologic diagnosis | 18/419 (4) | 5/140 (4) | 0.78 (0.28–2.17) | 0.63 |

* Odds ratios and P values were calculated with the use of multiple logistic-regression analysis. The covariates included in each model are given in the Supplementary Appendix. CI denotes confidence interval.

[†] Higher scores indicate worse functioning; a score of 4 or more was considered abnormal in slightly older children (mean age, 5.5 years).

[‡] A response of “yes” indicates a parent’s concern regarding the child’s development.

[§] The internalizing score summarizes the syndrome scales for “withdrawn,” “somatic complaints,” and “anxious/depressed.” The externalizing score summarizes the syndrome scales for “delinquent behavior” and “aggressive behavior.” A T score is classified as preclinical if it is at least 60 (approximately 1 SD above the mean) to 69 and clinical if it is at least 70 (approximately 2 SD above the mean).

shown). The three subjects in this group with G6PD deficiency who were examined performed normally on all tests.

Nine children in the hyperbilirubinemia group for whom formal evaluations were available had positive or trace-positive direct antiglobulin tests. The peak total serum bilirubin levels in these children ranged from 25.1 to 27.9 mg per deciliter (429 to 477 μmol per liter) and occurred at an earlier age than in the 61 subjects with negative direct antiglobulin tests (mean, 78 vs. 117 hours of age; $P=0.02$), but the estimated time required for the bilirubin level to decline was similar in these children. These 9 children performed less well on the WPPSI-R and VMI-4 than the 61 with negative direct antiglobulin tests; the adjusted absolute differences were -18.3 (95 per-

cent confidence interval, -26.6 to -10.1) for verbal IQ, -12.0 (95 percent confidence interval, -21.3 to -2.8) for performance IQ, -17.8 (95 percent confidence interval, -26.8 to -8.8) for full-scale IQ, and -14.3 (95 percent confidence interval, -27.9 to -0.6) for visual perception. There were no significant differences between children with positive direct antiglobulin tests and those with negative direct antiglobulin tests in results of the neurologic examination or according to the motor-performance checklist, but their parents were more likely to have answered “yes” in response to at least one item on the PEDS questionnaire (6 of 11 vs. 16 of 73, $P=0.03$). Only 2 children of the 39 in the control group who were tested had positive results on direct antiglobulin testing.

DISCUSSION

We found little evidence of adverse effects on neurodevelopment in children with a history of total serum bilirubin levels of 25 mg per deciliter or more, most of whom were treated with phototherapy alone, as compared with control subjects. Because most of those in the hyperbilirubinemia group had levels only slightly higher than 25 mg per deciliter, the power of the study to detect uncommon but catastrophic events, such as kernicterus, which occur at higher levels of total serum bilirubin, was limited, and our results cannot be generalized to higher levels than those studied. The results do, however, provide reassurance that more common possible adverse effects of hyperbilirubinemia, such as mild cognitive, behavioral, or motor impairment, are unlikely to occur in newborns with elevated bilirubin levels in the range we studied.

Our results differ from the findings of Soorani-Lunsing et al.,⁹ who reported an increase in minor neurologic dysfunction at 3 and 12 months in 20 infants with a history of nonhemolytic hyperbilirubinemia and total serum bilirubin levels of 13.6 to 26.0 mg per deciliter (233 to 445 μmol per liter). This difference may result from the fact that minor dysfunction recognizable in infancy may no longer be apparent by the age of five years. In the Collaborative Perinatal Project,^{27,28} examinations at the age of seven years were available for 52 of 68 subjects with total serum bilirubin levels of 25 mg per deciliter or more.²⁸ IQs were not affected, and none of the neurologic examinations were rated as definitely abnormal, results similar to those in our study. However, the proportion of subjects rated as having abnormal or suspicious results was significantly higher among those with a maximal total serum bilirubin level of 20 mg per deciliter or more than among those with levels below 20 mg per deciliter (22.4 percent vs. 15.1 percent, $P=0.001$), suggesting an increase in the risk of subtle abnormalities not found in our study.

We observed lower IQs in the subgroup of children with total serum bilirubin levels of 25 mg per deciliter or more who had positive direct antiglobulin tests. This finding must be interpreted with caution, however, because of the small sample (nine children). Although some studies have reported lower IQs in children with isoimmunization, as compared with older sib-

lings²⁹ or nonjaundiced controls,¹¹ other larger studies have not.^{27,30,31} One study linking perinatal records to premilitary examinations⁷ found lower IQs only among the subjects with positive direct antiglobulin tests whose hyperbilirubinemia was prolonged (≥ 5 days), but included only seven such subjects. Another study reported an increase in the risk of IQ below 85 (but no effect on mean IQ) in male children with negative direct antiglobulin tests and total serum bilirubin levels of 20 mg per deciliter or more.⁸ If there is an effect on cognition of total serum bilirubin levels of 25 to 28 mg per deciliter (479 μmol per liter) in infants with positive direct antiglobulin tests, it is likely to be smaller than what we observed. The 2004 American Academy of Pediatrics guideline² recommends phototherapy at total serum bilirubin levels lower by 2 to 3 mg per deciliter (34 to 51 μmol per liter) in infants who have hemolytic disease than in other infants.

The main limitation of our study is the inability to perform formal evaluations for all eligible subjects. Besides reducing the sample size, the selective participation of eligible subjects could have resulted in the appearance of more favorable outcomes in the hyperbilirubinemia group, if control subjects who were more impaired or children with hyperbilirubinemia who were less impaired were more likely to participate. It is reassuring that 94 percent of the eligible subjects in the hyperbilirubinemia group had follow-up to at least two years of age, by which time cerebral palsy should be apparent.³² For 22 percent of subjects, we relied on diagnoses in electronic records, which might not be complete. However, another report for which the same electronic database for case ascertainment was used³³ found a prevalence of cerebral palsy similar to that reported in other studies,^{34,35} suggesting that this ascertainment method is reasonable, at least with respect to cerebral palsy. It is also reassuring that the results of the neurologic examinations favored the hyperbilirubinemia group and that mean scores on standardized testing in this group were within national norms. However, we cannot rule out the possibility that differential participation affected our results, particularly with regard to subtle deficits that might not be captured in electronic records.

Our results have important implications for the management of jaundice, particularly among infants with negative direct antiglobulin tests. Although these data cannot be used to establish

a total serum bilirubin level at which the benefits of exchange transfusion exceed the risks, they do suggest that the level will generally be more than 25 mg per deciliter, since most children involved in our study who had total serum bilirubin levels between 25 and 30 mg per deciliter were treated with phototherapy alone and had no appreciable sequelae. The results also provide reassurance to families and clinicians that with prompt treatment, even very elevated serum bilirubin levels within the range observed in the study are not likely to result in long-term adverse effects on neurodevelopment.

Supported by grants from the National Institute of Neurological Diseases and Stroke (RO1 NS39683, to Dr. Newman) and the National Institutes of Health (M01 RR01271, to the University of California, San Francisco, Pediatric Clinical Research Center).

Presented in part at an advisory committee meeting of the Food and Drug Administration, June 11, 2003; at a conference on kernicterus sponsored by the National Institute of Child Health and Human Development, July 21, 2003; at the Pediatric Academic Societies Meeting, San Francisco, May 2, 2004; and at the American Academy of Pediatrics Annual Meeting, San Francisco, October 9, 2004.

Dr. Newman reports having served as a consultant in legal cases related to neonatal jaundice. Dr. Jeremy reports having served as a consultant in a single such case. No other potential conflict of interest relevant to this article was reported.

We are indebted to Pete Dorin, Ayawanna Smith, and Sandy Hammonds for research assistance; to Michael Kohn for database development; to Blong Xiong for programming; to M. Jeffrey Maisels for consultation throughout the project; to the other members of the JIFee study team for their contributions, including Pilar Bernal, Russell Reiff, Jean Hayward, Amer Khan, Philip Sankar, Richard Friedrich, Steven Miller, Jonathan Strober, Karl Buddenhagen, Gary Rezowalli, Lynn Calonico, and Pamela Braswell; and to Giovanna Spinella, the project officer of the study.

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