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# Onset of Jaundice in Glucose-6-Phosphate Dehydrogenase-Deficient Neonates

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**ABSTRACT.** *Objective.* We asked whether neonatal jaundice associated with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency commences either in utero or in the immediate postnatal period and whether this perinatal bilirubinemia is the precursor of the subsequent neonatal jaundice and hyperbilirubinemia.

*Methods.* Mandatory serum total bilirubin (STB) determinations were performed within 3 hours of birth, to reflect the in utero state (first STB), and on the third day of life (second STB), with additional determinations as clinically necessary, on healthy, term male neonates at high risk for G-6-PD deficiency. G-6-PD Mediterranean mutation was determined by molecular means. G-6-PD-deficient neonates were compared with control participants. The relationship of first STB values to second STB and subsequent hyperbilirubinemia (defined as STB  $\geq 256 \mu\text{mol/L}$  [15.0 mg/dL]) was determined.

*Results.* Both first and second STB values were significantly higher in the G-6-PD-deficient neonates ( $n = 52$ ) than in control participants ( $n = 166$ ;  $50 \pm 12 \mu\text{mol/L}$  vs  $44 \pm 10 \mu\text{mol/L}$  [ $2.9 \pm 0.7 \text{ mg/dL}$  vs  $2.6 \pm 0.6 \text{ mg/dL}$ ] and  $174 \pm 52 \mu\text{mol/L}$  vs  $152 \pm 52 \mu\text{mol/L}$  [ $10.2 \pm 3.1 \text{ mg/dL}$  vs  $8.9 \pm 3.0 \text{ mg/dL}$ ] for the first and second STB values, respectively). The rate of rise between these 2 points was greater in the G-6-PD-deficient neonates ( $2.6 \pm 0.9 \mu\text{mol/L/h}$  vs  $2.2 \pm 0.9 \mu\text{mol/L/h}$  [ $0.15 \pm 0.05 \text{ mg/dL/h}$  vs  $0.13 \pm 0.05 \text{ mg/dL/h}$ ]). Sixteen (30.8%) of the G-6-PD-deficient neonates developed hyperbilirubinemia compared with 10 (6%) of control participants (relative risk: 5.11; 95% confidence interval: 2.47–10.56). In both G-6-PD-deficient and normal populations, first STB values correlated significantly with both second STB values and with those who subsequently developed hyperbilirubinemia. Significantly more G-6-PD-deficient neonates with a first STB value greater than or equal to the mean developed hyperbilirubinemia compared with those with first STB less than the mean: 13 of 28 neonates versus 3 of 24 (relative risk: 3.7; 95% confidence interval: 1.20–11.51). This difference did not reach statistical significance in the control group.

*Conclusions.* Higher first STB values, an increased risk of hyperbilirubinemia in G-6-PD-deficient neonates with first STB value greater than or equal to the mean, and significant correlation between first STB values and second STB values and hyperbilirubinemia suggest that jaundice in G-6-PD-deficient neonates commences in

the immediate perinatal period, most likely in utero. *Pediatrics* 2001;108:956–959; *bilirubin, jaundice, hyperbilirubinemia, glucose-6-phosphate dehydrogenase deficiency, perinatal, in utero.*

ABBREVIATIONS. STB, serum total bilirubin; G-6-PD, glucose-6-phosphate dehydrogenase; CI, confidence interval.

An association between umbilical cord blood bilirubin levels, reflecting the in utero state, and serum total bilirubin (STB) values in early neonatal life has been recognized in some neonates for many years.<sup>1</sup> This concept has been used reliably in the prediction of hyperbilirubinemia attributable to Rh isoimmunization.<sup>2</sup> Although the success in identifying infants who are at risk for subsequent development of hyperbilirubinemia has not been universal,<sup>3,4</sup> in some series of ABO incompatibility<sup>5–7</sup> and also in nonhemolytic conditions,<sup>8–11</sup> use of umbilical cord blood STB determination has shown some success in the prediction of severe jaundice. These observations suggest that neonatal jaundice frequently—but not consistently—has its origins in utero.

Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is a commonly occurring enzyme defect that is associated with a high incidence of severe neonatal hyperbilirubinemia with the potential of irreversible bilirubin encephalopathy if not treated in time.<sup>12</sup> The pathogenesis of this hyperbilirubinemia is different from that in G-6-PD-normal neonates: decreased bilirubin conjugation, the result of an interaction between G-6-PD deficiency and promoter polymorphism of the gene that controls the bilirubin conjugating enzyme UDP glucuronosyltransferase, is a crucial factor.<sup>13,14</sup> To elucidate further the pathogenesis of the associated bilirubinemia, we therefore asked whether the jaundice associated with the G-6-PD Mediterranean mutation, as in some other conditions, commences in the perinatal period and whether this in utero or very early bilirubinemia is the precursor of subsequent jaundice or hyperbilirubinemia in these neonates.

## METHODS

### Study Protocol

The study was approved by the Institutional Review Board of the Shaare Zedek Medical Center. A cohort of consecutively born healthy boys who were born at  $\geq 37$  weeks' gestation at the Shaare Zedek Medical Center to Sephardic Jewish mothers whose families originated in Asia Minor were studied. This subgroup of the Israeli population has been shown to have an exceptionally high

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incidence of G-6-PD deficiency.<sup>15,16</sup> Blood was drawn for mandatory STB determinations within the first 3 hours after birth, to reflect the in utero status (first STB), and again at the time of routine metabolic screening on the third day of life (second STB). Simultaneously with 1 of these determinations, blood was collected for DNA extraction.

Routine medical care for these neonates included screening for G-6-PD deficiency on the first day of life, blood group determination, and direct Coombs' testing for infants born to Rh-negative or O blood group mothers. Infants were monitored visually as inpatients by our medical and nursing staff for the development of jaundice with additional STB determinations if warranted clinically. Those with a second STB value  $\geq 50$ th percentile for hour of life<sup>17</sup> and therefore at high risk for subsequent hyperbilirubinemia were scheduled to be followed as outpatients, whereas those with lower predischarge STB values, at low risk for hyperbilirubinemia, were evaluated at well-infant clinics or by family pediatricians or ritual circumcisers (mohel) and referred for evaluation if deemed necessary. Finally, any parent who had any doubt as to their infant's jaundice status was able to return for an STB at any time during the first week of life. The patient compliance in our population was excellent, and we are confident that we were aware of virtually all infants with an STB  $\geq 256$   $\mu\text{mol/L}$  (15.0 mg/dL). These neonates were followed by us until stabilization of the STB values. When phototherapy became necessary after discharge, the infants were readmitted to our unit. Phototherapy was commenced in G-6-PD-deficient newborns when STB values exceeded 15.0 mg/dL. Breastfeeding was encouraged, although mothers were warned of the dangers of eating fava beans or taking drugs known to be triggers of hemolysis in G-6-PD-deficient individuals while nursing. Infants with any other condition that was likely to exacerbate hyperbilirubinemia, such as cephalhematoma, direct Coombs'-positive isoimmunization, maternal diabetes, sepsis, or Down's syndrome, were excluded from the study.

### Laboratory Methods

DNA was extracted from peripheral blood leukocytes using a high-salt extraction procedure.<sup>18</sup> For G-6-PD genotyping, DNA was shipped to The Scripps Research Institute (La Jolla, CA) for molecular classification. Polymerase chain reaction followed by allele-specific oligonucleotide hybridization was used to determine the presence or absence of nt 563, the nucleotide mutated in G-6-PD Mediterranean.<sup>19</sup> Details of the procedure have been published elsewhere.<sup>13</sup>

STB values were determined by reflectance spectrophotometry using an Ektachem analyzer (Vitros 700c/750XRC Chemistry System; Johnson and Johnson Clinical Diagnostics, Rochester, NY). Blood group determinations and direct Coombs' testing were performed by routine laboratory techniques.

### Data Analysis

The G-6-PD genotype was used to classify the infants into G-6-PD-deficient hemizygote (study) and normal hemizygote (control) groups. Hyperbilirubinemia was defined as a serum total bilirubin  $\geq 256$   $\mu\text{mol/L}$  (15.0 mg/dL) in the first week of life, for standardization with our previous studies.<sup>13,17</sup> Results were compared using Student *t* test,  $\chi^2$  analysis, or linear correlation, as appropriate. Significance of these tests was determined as  $P < .05$ . Evaluation of the effect of either G-6-PD deficiency or first STB greater than or equal to the mean value on the subsequent development of hyperbilirubinemia was determined by calculating the relative risk and 95% confidence intervals (CI). Significance in these cases was defined as a 95% CI range that did not include the digit 1. Rate of rise of STB was calculated as the difference between the first and second STB values divided by the number of hours between these tests.

## RESULTS

A total of 225 infants were enrolled in the study. Seven (6 Coombs' positive, 1 maternal diabetes) were recognized not to meet study criteria after enrollment. Thus, the cohort that met study criteria comprised 218 infants, 52 of whom were hemizygotes for G-6-PD Mediterranean 563T and 166 of whom did not have this mutation. Demographic data for these

infants are summarized in Table 1. Despite that significantly fewer G-6-PD-deficient neonates were nursed (Table 1), 16 (30.8%) of the G-6-PD-deficient neonates developed hyperbilirubinemia, compared with 10 (6%) of the control participants (relative risk: 5.11; 95% CI: 2.47–10.56;  $P < .0001$ ).

Results of the first and second STB tests (mean  $\pm$  SD) and the age at sampling are summarized in Table 2. Despite the similarity in times of sampling between study and control groups, both first and second STB values and the rate of rise between these 2 determinations were significantly higher in the G-6-PD-deficient neonates than in the control group.

In both G-6-PD-deficient and control groups, first STB values correlated with second STB values ( $r = 0.6$ ,  $P < .0001$  and  $r = 0.5$ ,  $P < .0001$  for the G-6-PD-deficient and control infants, respectively), with those who developed serum bilirubin values  $\geq 256$   $\mu\text{mol/L}$  (15.0 mg/dL;  $r = 0.34$ ,  $P = .01$  and  $r = 0.21$ ,  $P = .01$ , respectively), and with the rate of rise ( $r = 0.56$ ,  $P < .0001$  and  $r = 0.39$ ,  $P < .0001$ , respectively).

In the G-6-PD-deficient cohort, a significantly greater number of neonates among those with a first STB value greater than or equal to the mean developed hyperbilirubinemia compared with those with a first STB less than the mean: 13 (46%) of 28 neonates versus 3 (12.5%) of 24 neonates (relative risk: 3.7; 95% CI: 1.20–11.51;  $P = .02$ ). This difference did not reach statistical significance in the control group: 9 (9.6%) of 94 versus 1 (1.4%) of 72, respectively (relative risk: 6.89; 95% CI: 0.89–53.18;  $P = .06$ ).

## DISCUSSION

Some studies of umbilical cord blood bilirubin values have shown that both nonhemolytic jaundice<sup>8–11</sup> and hemolysis attributable to Rh isoimmunization<sup>2</sup> or ABO incompatibility<sup>5–7</sup> commence in utero. In these conditions, the cord blood bilirubin values correlate with subsequent hyperbilirubinemia and have been used to predict its severity. To understand further the pathophysiology of G-6-PD deficiency-associated neonatal jaundice, we studied its onset to determine whether it commences perinatally, ie, either during fetal life or in the immediate postnatal period, as in some hemolytic conditions noted above, or well into the neonatal period, as with other nonhemolytic bilirubinemias. In the current study, already immediately after birth, most likely reflecting the in utero status, the G-6-PD-deficient neonates had significantly higher serum bilirubin values than control participants. Significantly higher STB values were evident again on the third day. The

TABLE 1. Demographic Data of the Infants Studied

	G-6-PD Deficient	Control	Significance
<i>n</i>	52	166	
Birth weight (g)	3189 $\pm$ 462	3316 $\pm$ 457	NS
Gestational age (wk)	39.0 $\pm$ 1.5	39.5 $\pm$ 1.0	NS
Vaginal delivery (%)	80.8	92.7	$P = .02$
Exclusively breastfed (%)	50	74.7	$P = .001$

Values are mean  $\pm$  standard deviation or percentages, as appropriate.

NS indicates not significant.

**TABLE 2.** Values for First and Second STB, Age at Sampling, Rate of Rise of Serum Bilirubin, and the Incidence of Hyperbilirubinemia

	G-6-PD Deficient (n = 52)	Control (n = 166)	Significance
Age at 1st sample (h)	1.7 ± 1.0	1.9 ± 0.7	NS
1st STB (μmol/L [mg/dL])	50 ± 12* [2.9 ± 0.7*]	44 ± 10 [2.6 ± 0.6]	P = .003
Age at 2nd sample	53 ± 10	52 ± 8	NS
2nd STB (μmol/L [mg/dL])	174 ± 54* [10.2 ± 3.1*]	152 ± 52 [8.9 ± 3.0]	P = .007
Rate of bilirubin rise (μmol/L/h) [mg/dL/h]	2.6 ± 0.9* [0.15 ± 0.05*]	2.2 ± 0.9 [0.13 ± 0.05]	P = .01
Hyperbilirubinemia (n)	16 (30.8%)	10 (6.0%)	P < .0001

Values are mean ± standard deviation or percentage, as appropriate. NS indicates not significant.

rate of rise of STB and the incidence of hyperbilirubinemia were similarly increased in the G-6-PD-deficient neonates compared with control participants.

Higher umbilical cord blood STB levels<sup>20,21</sup> or increased STB values on the first day of life<sup>22,23</sup> have been shown in previous studies of G-6-PD-deficient neonates, suggesting either in utero or a very early postnatal onset of jaundice. However, as there was no attempt at correlation between this early bilirubinemia and subsequent jaundice in these studies, it cannot be concluded that the former was the forerunner of hyperbilirubinemia. Our demonstration of a significant correlation between very early STB values and later bilirubin values and the significantly higher relative risk of first STB result greater than or equal to the mean in the subsequent development of hyperbilirubinemia now demonstrates that this perinatal bilirubinemia is the precursor of subsequent jaundice and hyperbilirubinemia.

Although umbilical cord blood sampling undoubtedly would have offered a more accurate representation of the in utero status, for logistical reasons and because of difficulties in coordinating the study with the delivery room staff, we chose to obtain samples from the infants within 3 hours of delivery to reflect the in utero situation. Although we cannot exclude categorically a very early postnatal onset of the bilirubinemia, we are confident that this method of sampling reliably reflected the in utero state. Presuming that the hourly rates of rise during the first days of life reflected the rise during the first 3 hours of life as well, the first STB values should have been only marginally elevated over the actual cord blood values and should not have affected the comparisons between the study and control groups to any major degree. The slightly higher but clinically insignificant mean first STB values for the control groups than those reported by others for cord blood samples may represent a combination of the timing of the sample and interlaboratory variation between our laboratory's STB determination and those that have been used by other laboratories in the past.<sup>24</sup>

Although the current and previous studies showed that umbilical cord or first-day STB determinations<sup>25</sup> may have some predictive value for the subsequent development of hyperbilirubinemia, the aim of this study primarily was to shed light on the pathophysiology of G-6-PD deficiency-associated neonatal jaundice. It was not designed as a study of prediction of subsequent hyperbilirubinemia and should not be interpreted as such. Accurate prediction can be accomplished by predischarge STB test-

ing at the time of metabolic screening, as recently described both for normal<sup>26</sup> and G-6-PD-deficient<sup>17</sup> newborn populations.

G-6-PD deficiency is estimated to affect hundreds of millions of people not only in areas in which the condition is indigenous but also with a potential for serious complications in North America.<sup>27</sup> Awareness of the condition and its dangers and an understanding of the differing pathophysiology of the associated jaundice compared with that of G-6-PD-normal individuals are essential if the potential of bilirubin encephalopathy is to be limited.

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## THE GREAT TOOTH ROBBERY

“The night of 18 June 1815 was one to remember. After 23 years of war in Europe, Napoleon faced the combined might of England, Holland, and Prussia at Waterloo. By 10 pm, the battle was over. The French were defeated and 50,000 men lay dead or wounded on the battlefield. The casualties were high, but for one group of people that was reason to celebrate. They were the dentists who were about to benefit from the great tooth bonanza.

In the early part of the 19th century, patients with plenty of money, but few teeth were prepared to pay enormous sums for a good set of dentures. The best were made with real human teeth at the front. Most of the time demand for second-hand incisors far outstripped supply, but wars helped make up the shortfall. The windfall from Waterloo provided enough to ship supplies all round Europe and even across the Atlantic.”

Pain S. *New Scientist.* June 16, 2001

Noted by JFL, MD

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