Introduction
When the bilirubin concentration in the serum increases, bilirubin is deposited in the skin and subcutaneous tissues, (1) producing the (yellow) physical sign of jaundice or icterus. There is a well-established relationship between the total serum bilirubin (TSB) concentration and the intensity of jaundice, and the possibility of quantifying the bilirubin value by assessing skin color is not new. This relationship was documented in 1918 by Ypupö, (2) although he measured the bilirubin concentration in whole blood, not serum. The next major advance was the recognition that bilirubin could be toxic, that its toxicity was related to its concentration, and that it was possible to treat hyperbilirubinemia (and prevent neurologic damage) with exchange transfusion. (3) Pediatricians measured TSB in infants if jaundice appeared early (in the first 24 hours after birth) or appeared excessive for the infant’s age. Unfortunately, it is neither possible, nor desirable, to measure the serum bilirubin daily in every infant for the first week after birth. Accordingly, clinicians have used the clinical sign of jaundice as the trigger for deciding when to measure the TSB concentration.

The Clinical Diagnosis of Hyperbilirubinemia
How Good is the Visual Assessment of Jaundice?
Although there is a clear and semi-quantitative relationship between the yellowness of the skin and the TSB, the variations in color perception by the human eye, differences in neonatal skin pigmentation, and variations in both the intensity and color of the available light affect the ability to estimate the TSB by assessing the degree of jaundice in a newborn. In 1941, Davidson and associates (4) described their experience evaluating the degree of jaundice in 99 infants. They examined each infant in daylight, applying a tongue depressor to the mucous membrane of the lower jaw as well as the skin of the forehead or the chin. Based on the icterus they observed following this procedure, they assigned the infants to one of three categories: no jaundice, moderate jaundice, or marked jaundice. TSB measurements were obtained daily from heel stick samples. The results are shown in Figure 1. Of 99 infants examined, jaundice was noted on at least one occasion in 63 (64%) of the infants. (Hence, the oft-quoted figure that about two thirds of healthy newborns appear jaundiced during the first postnatal week.) The population studied was 90% white, but the number breastfed was not reported.

Although there was a clear relationship between the TSB and the clinical observations of no jaundice, moderate jaundice, or marked jaundice, there was a wide range of TSB values in each category. A few infants whose TSB concentrations were less than 5 mg/dL (85.5 mmol/L) were categorized as having marked jaundice. More importantly from the clinician’s perspective is that in about 5% of the observations, infants who were not jaundiced had TSB levels
between 10 and 12 mg/dL (171 and 205 μmol/L), and in some 10% of nonjaundiced infants, TSB levels were 8 to 10 mg/dL (137 to 171 μmol/L). Failure to recognize that an infant who has a TSB value of 10 mg/dL (171 μmol/L) is jaundiced is of no consequence in a 3- or 4-day-old infant, but it is a different matter if that infant is 24 or even 36 hours old, when a value of 10 mg/dL (171 μmol/L) is above the 95th percentile (6) and calls for further investigation, additional TSB measurements, and close follow up. (7) Wood and associates (8) found that “despite a general alertness for jaundice,” infants with TSB values above 12 or even 15 mg/dL (205 to 257 μmol/L) were not always identified as being jaundiced.

More recent studies confirm these earlier observations (Fig. 2). (9),(10) Moyer and colleagues (10) found that experienced residents, nurse practitioners, and attending physicians provided wide ranges of estimates of TSB concentrations. In addition, agreement between observers was very poor regarding which areas of the body were jaundiced and the estimated TSB. On the other hand, four Israeli neonatologists provided acceptable estimates of TSB concentrations in 283 term newborns. (11) Cephalocaudal Progression of Jaundice

A potentially useful refinement in the clinical assessment of jaundice is the observation that jaundice appears initially in the face of a newborn and as the TSB increases, becomes apparent on the chest and abdomen and finally, in the extremities (Fig. 3). (12) an observation that has been confirmed using transcutaneous bilirubin (TCB) measurements. (13) (14) Knudsen (14) postulated that the cephalocaudal progression of jaundice can be explained by conformational changes of bilirubin albumin complexes. Although the initial binding of bilirubin to albumin is extremely rapid, final conformational changes may not occur for about 8 minutes. Thus, blood leaving the reticuloendothelial system and going to the proximal parts of the body contains bilirubin that is less tightly bound to albumin than that which subsequently reaches the distal parts of the body. Bilirubin that is less tightly bound is more likely to precipitate as bilirubin acid in phospholipid membranes in the skin and subcutaneous tissues, which is why the face appears jaundiced before the abdomen or the legs.

As can be seen from Figure 3, although mean indirect bilirubin levels increase as jaundice progresses from the head to the extremities, the range of bilirubin values in each zone is wide. Bhutani and associates (15) studied 916 infants in six well-baby nurseries. The infants were evaluated by experienced nurses and, if jaundice was present, the zone was noted. At the same time, TCB was measured. The cephalocaudal progression was confirmed, but the ranges of TCB and the overlap were substantial. In zone 1, TCB values ranged from 2.3 to 13.8 mg/dL (39 to 236 μmol/L) and in zone 2 from 4.3 to 14.2 mg/dL (74 to 243 μmol/L).

Comparison With a Color Scale

One method of improving the estimate of TSB values by eye is to compare the infant’s skin color with a color scale. In 1960, Gosset (16) described the use of an iometer (Cascade Healthcare Products, Salem, Ore.) to assess neonatal jaundice. It appears that Dr Gosset painted transverse stripes of five different shades of yellow on a piece of
Noninvasive Measurements of Bilirubin
Skin Reflectance and Transcutaneous Bilirubinometry
When light is transmitted to the skin, the yellowness of the reflected light can be measured to provide an objective measurement of skin color. Hennemann and coworkers (22, 23) applied these principles to predict TSB levels from skin reflectance. Monochromatic light from a tungsten source was applied to the infant’s skin through one branch of a bifurcated fiberoptic bundle while a second branch of the bundle carried the reflected light back to an optical detector. The transduced signals were recorded and processed in a computer. This system was too complex for routine use in the nursery.

The first clinically applicable and easily portable transcutaneous bilirubinometer was introduced by Yamamouchi and associates. (24) Working with the Minolta Camera Company, these investigators developed a hand-held instrument that measured the yellow color intensity in the skin. When a photoprobe is pressed against the infant’s skin to a pressure of approximately 200 g, a xenon tube produces a strobe light that travels through a fiberoptic filament to the photoprobe (Fig. 5). The bright light penetrates the blanched skin and transilluminates the subcutaneous tissue. The scattered light returns through a second fiberoptic filament and is carried to the spectrophotometric module. Inside the module, the light is divided by a dichroic mirror into two spectra, one of which passes through a blue filter (maximum absorption, 460 nm) and the other through a green filter (maximum absorption, 550 nm). Absorption at these spectra correct for hemoglobin, and the intensity of the yellow color is measured as the difference between the optical
Figure 3. Zones for estimating the cephalocalvarial progression of jaundice. The indirect bilirubin values corresponding to each zone are shown in the table. Reprinted with permission from Kramer (12), copyright © 1969, American Medical Association.

<table>
<thead>
<tr>
<th>Dermal Zone</th>
<th>Indirect Bilirubin (mg/100 ml)</th>
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<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>1</td>
<td>5.9 ± 6.3</td>
</tr>
<tr>
<td>2</td>
<td>8.9 ± 1.7</td>
</tr>
<tr>
<td>3</td>
<td>11.8 ± 1.8</td>
</tr>
<tr>
<td>4</td>
<td>15.0 ± 1.7</td>
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<tr>
<td>5</td>
<td>&gt; 15</td>
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densities of blue and green and processed electronically to provide a digital meter reading.

Multiple studies performed with the Minolta jaundice meter have demonstrated a linear relationship between TSB and TcB measurements, (25)(26)(27)(28) and the meter has been used to document the previously described cephalocalvarial progression of jaundice in the newborn. (13)(14) These studies demonstrated that the jaundice meter could provide an objective measurement of the degree of newborn jaundice and, when used as a screening tool, could identify infants who required a TSB measurement. (25)(26)(27)(28) Routine use of this meter in the nursery reduced costs and the need for TSB measurements. (29)(30) Nonetheless, both the original jaundice meter and the subsequent model had some disadvantages. They did not provide a read-out of the serum bilirubin concentration; a TcB index was displayed and TSB values were derived from the TcB index on the basis of data obtained in individual hospital laboratories. Further, readings were significantly altered by gestation and skin pigmentation. As a result, these instruments have achieved limited acceptance in hospitals in the United States, although they were widely used in Japan. (27)(31)(32)

Tayaba and associates (9) evaluated the Chromatix Colormate III (Chromatics Colormate International, Inc., New York, NY) in a large population of term and preterm infants. The handheld colorimeter, which contained a xenon flash tube and light sensors connected to a portable computer, measured over a band of wavelengths from 400 to 700 nm, with specific filters used to assess the reflectance of light for specific wavelengths. The algorithm incorporated the underlying color of normal skin, accounting for it in a baseline evaluation. Measurements made on the cheek, back, forehead, and chest showed a close correlation with TSB measurements. (9) The primary disadvantage was the requirement for a baseline measurement of skin color in every infant before the onset of jaundice. This instrument no longer is marketed.

Contemporary Instruments for TcB Measurement

Two handheld devices that use skin reflectance currently are available for the measurement of TcB: the BiliCHEK® (Respirronics, Marietta, GA.) (33)(34) and the Draeger JM-103 (formerly the Minolta/Hill-Rom AirShields JM-103) (Draeger Medical, Hatboro, Pa.). (35)(36) Although these instruments use different algorithms and measurement techniques, their principles of operation are similar. The BiliCHEK measures TcB by using the entire spectrum of visible light (580 to 760 nm) reflected by the skin. White light is transmitted into the skin, and reflected light is collected for analysis (Fig. 6). Algorithms have been developed that take into account the effect of hemoglobin, melanin, and dermal thickness, and the absorption of light due to bilirubin in the capillary and subcutaneous tissue is isolated by spectral subtraction. The JM-103 has attempted to overcome some of the disadvantages of the earlier model by using two wavelengths and a dual optical path system. (35) The principle of operation includes the formation of two beams, one of which reaches only the shallow areas of the subcutaneous tissue, while the other penetrates the deeper layers. The differences between the optical densities are detected by blue and green photocells. Measurement of bilirubin accumulated primarily in the deeper subcutaneous tissue should decrease the influence of other pigments in the skin, such as melanin and hemoglobin. It was hoped that the innovative technologies employed in the BiliCHEK and the JM-103 would make TcB measurements independent of race, age, gestation, and birthweight, but these hopes have not been fully realized. Both instruments pro-
vide a digital read-out of the actual transcutaneous bilirubin concentration rather than an index that needs to be converted to a TSB value. The BiliChek requires five repeat measurements that are averaged to provide one TcB measurement. The JM-103 provides the option of obtaining one to five measurements that are automatically averaged.

Factors Affecting the Measurement

Effects of Skin Pigmentation and Gestation

Although large studies of both the BiliChek and the JM-103 have shown very good correlations between TcB and TSB measurements, (33)(34)(36)(37) the hope that such measurements would be independent of both race and gestation has not been entirely fulfilled. In the one study that contained a significant number of African-American infants (n=145), (35) the correlation between BiliChek TcB and high-performance liquid chromatography (HPLC) measurements of the TSB in African-American infants was as good as in Caucasian infants, but TcB measurements by the JM-103 in African-American infants tended to overestimate the TSB measurements. (36) In the other racial groups (East Asian, Middle Eastern, Indian/Pakistani, Hispanic), JM-103 measurements were very similar to the TSB measurements. (36) Nevertheless, both the JM-103 and the BiliChek are less reliable in predicting TSB in more preterm infants, particularly those younger than 30 weeks' gestation. (37)(38)(39)

Site of Sampling

In 77 Japanese infants, JM-103 measurements from the forehead correlated well with TSB measurements and better than measurements obtained with the JM-102. (35) We compared JM-103 measurements from the forehead and sternum in 475 infants and found that the Pearson correlation coefficient (r) was higher for the sternum (0.953) than the forehead (0.914). (36) Because the forehead is exposed to ambient light, both in the nursery and following discharge (while the sternum almost always is covered), measurements from the sternum might be a better choice.

Studies with the BiliChek have used both forehead (33)(34) and sternum as sampling sites. (37) Engle and associates (40) studied a Hispanic population and found that BiliChek measurements from the forehead tended to underestimate TSB, particularly when the TSB exceeded 10 mg/dL (171 mmol/L). However, in a small study of 21 infants comparing outpatient BiliChek measurements from the brow and the sternum, Poland and associates (41) found that brow readings were 20% lower than TSB values, but chest readings were only 5% lower. They
suggested that exposure to ambient light might result in lower TcB readings. On the other hand, Ebbezen and colleagues, (37) in their study of Danish infants, found that BiliChek measurements from the forehead in a neonatal intensive care unit popula-

tion predicted the TSB better than measurements from the sternum; in the well baby population, measurements at both sites were equally reliable. They also found, as did Engle, (40) that the BiliChek tended to underestimate the TSB, a discrepancy that increased when the TSB was 10 mg/dL (171 mcmmol/L) or greater.

**Laboratory Measurements and TcB**

TcB is a measurement of bilirubin in the skin, not the serum. Currently, we use the TSB value for making decisions about when to initiate investigations, what type of surveillance is necessary, and when to initiate treatment. (7) Some investigators have compared TcB measurements with HPLC measurements of serum bilirubin; (33) others have compared the TcB measurement with standard laboratory measurements of TSB. The variability of TcB measurements within and between different laboratories is well documented, (42) so that comparisons with TcB measurements vary in different institutions. In addition to these variations, we occasionally have laboratory errors. Indeed, we have had occasions in our nursery where the measured TSB diverged widely from the TcB. When the laboratory test was repeated, the initial measurement was shown to be in error.

HPLC measurements sometimes are considered the putative “gold standard” for measuring serum bilirubin, and in one study, (34) BiliChek TcB measurements correlated more closely than did standard laboratory TSB measurements with HPLC TSB measurements. On the other hand, no data document the variability of HPLC measurements within or between different laboratories; the assumption that this is the gold standard against which TcB measurements should be compared remains to be proven.

**Phototherapy**

Because phototherapy bleaches the skin, both visual assessments of jaundice and TcB measurements in in-
BiliChek Schematic

Figure 6. Schematic diagram of the BiliChek® TcB meter. Reproduced with permission from Respirationics.

...patients undergoing phototherapy are not reliable but probably can be taken about 18 to 24 hours after cessation of phototherapy. (39)(43)

Who is Doing the Measurement?

Virtually all of the published studies performed with the BiliChek and the JM-103 have been performed under the relatively rigorous conditions of clinical investigation, with TcB measurements obtained by research nurses or technicians. Such studies almost certainly provide more accurate and precise results than those obtained with "real world" measurements by many different nurses or physicians in different environments and in the course of a normal day's work.

Impact of TcB on Blood Sampling and Costs

We and others have shown a significant reduction in TSB measurements in our nurseries when TcB measurements were used as a screening tool. (29)(44) Currently, every infant in our nursery is screened with a JM-103 TcB measurement during the midnight shift. This has resulted in a decrease in the number of infants who have at least one TSB measurement during their nursery stay from 27.6% to 9%, which represents a 67% reduction in TSB measurements. Ebbesen and associates (37) estimated that TcB measurements in their nursery would save 80% of the infants from blood sampling.

How Should We Use TcB Measurements?

At present, TcB measurements should be used as a screening tool. They can help to answer the questions "Should I worry about this infant?" and "Should I obtain a TSB on this infant?" (45) Our primary goals are to avoid an unnecessary heel stick and to avoid missing a high TSB level (ie, a false-negative TcB measurement). To achieve these goals, we can set a value for a TcB measurement (based on the infant's age in hours and other risk factors) above which a TSB level always should be obtained.

In Ebbesen's nursery, (37) if the TcB value is 70% of the TSB level recommended for the use of phototherapy, a TSB measurement is obtained. In our nursery, the nurses automatically obtain a TSB if the TcB is above the 75th percentile. (6) Although we readily accept the likelihood that we will obtain several unnecessary TSB measurements, we do not want to miss a TSB level that will change our management. In our study with the JM-103, (38) the chance of a TcB measurement underestimating the TSB level by 3 mg/dL (51 mcMol/L) or more was only 0.6%, so choosing the 75th percentile as a cut point seemed reasonable.

Bhutani and colleagues (38) found that as long as the TcB was less than the 75th percentile, 0 of 349 infants had a TSB above the 95th percentile (a negative predictive value of 100%).

An alternative approach is: If the real TSB value is TcB + 3 mg/dL (51 mcMol/L), is there a reasonable chance that this will change my management? If the answer is yes, a TSB should be measured, which allows the clinician to take into account other risk factors, including the gestation. With this approach, no infant who has significant hyperbilirubinemia should be missed, and many infants and their families will be spared the trauma, cost, and inconvenience of having a laboratory measurement of serum bilirubin. In an outpatient study of a primarily Hispanic population, no infant who had a JM-103 level of 13 mg/dL (222 mg/dL) or less had a TSB of greater than 17 mg/dL (291 mcMol/L), (46) and 50% of TSB determinations were avoided.

Conclusion

Although TcB measurements provide a good estimate of the TSB level,
they are not a substitute for TSB values, and they never should be considered in isolation. Further, critical decisions should not be made from a single TcB measurement. Any measurement has the potential for error, and if the clinical assessment of jaundice differs from the TcB reading, a TSB should be measured.

Measurements of TcB in the nursery, the office, or other outpatient settings, including the home, provide a noninvasive, instantaneous estimate of the TSB. This has been of enormous value in our nursery as well as in our outpatient follow-up clinic, and should prove equally valuable in an office practice. TcB measurements can help to avoid the potential errors associated with clinical estimation of bilirubin levels.

Unfortunately, because of cost concerns, very few pediatric offices are currently equipped with an instrument for measuring the TcB. The CPT code for measuring TcB is 88400. A private pediatric group affiliated with our hospital found that about 50% of 250 TcB measurements performed in the office were reimbursed by third party payers at an average of about $6 per test. (S. Clune MD, personal communication.)

Before we had pulse oximetry, we assessed the oxygen saturation of a newborn or a child who had asthma by eye, and we were often wrong. Today, it is difficult to imagine managing such children without the benefits of pulse oximetry. It is likely that TcB measurements soon will be considered similarly indispensable in the care of the jaundiced newborn.

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