

Blue Light, Green Light, White Light, More Light: Treatment of Neonatal Jaundice

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Iron protoporphyrin, better known as heme, is essential to life, because of both its ability to transport and release molecular oxygen and its catalytic function in several important enzymes. When its usefulness is over, it could be simply excreted into the bile. If this were done, however, an essential element, iron, would also be lost. Thus, a catabolic pathway has evolved (or was created, depending on one's viewpoint) to conserve the iron moiety and get rid of the protoporphyrin. This iron salvage pathway involves two steps. In the first and rate-limiting step catalyzed by the enzyme heme oxygenase, the closed protoporphyrin ring is opened at the α -methine bridge. This yields three products from heme: free iron, carbon monoxide, and the blue-green pigment biliverdin IX α (IX designates this pigment as a derivative of protoporphyrin IX; the α is from the fact that the closed protoporphyrin ring is cleaved at the α -carbon⁴⁶). The iron is salvaged, and the carbon monoxide is excreted by the lungs, leaving biliverdin IX α . This pigment, like the parent heme, is readily excreted into the bile. In all mammals, however, biliverdin is further metabolized in a reduction reaction (i.e., energy-requiring step) to form bilirubin IX α . Until recently no obvious reason existed for this conversion of a readily-excreted, nontoxic molecule (biliverdin) into a poorly excreted, toxic molecule (bilirubin), which must be further metabolized to be excreted. Two possible explanations have appeared. One is the finding that biliverdin is only slowly transported by the placenta³³; thus if biliverdin were the end product of heme catabolism, it would be trapped on the fetal side in utero (yielding fluorescent blue-green babies). An even more interesting finding is that bilirubin is a potent antioxidant, effectively scavenging peroxy radicals.^{47,48} Thus, moder-

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ately increased bilirubin levels in the newborn period *may* be physiologically beneficial.

Normally, bilirubin is conjugated to glucuronic acid by the liver and excreted in the bile. Fetuses, however, do not conjugate bilirubin; instead, fetal bilirubin is cleared by the placenta and excreted by the mother. During the immediate newborn period, until the conjugating ability of the liver is sufficient, elevated levels of bilirubin are so common as to be termed "physiologic" jaundice.²⁷ Any factor that increases the bilirubin load, most commonly from hemolysis, can lead to levels of bilirubin of clinical concern. It has long been recognized that high levels of bilirubin cause irreversible brain damage and even death (kernicterus).⁸ As a result of the aggressive treatment of hyperbilirubinemia, either mechanically (i.e., exchange transfusion) or photochemically (i.e., phototherapy), kernicterus is now rare. More moderate elevations of bilirubin have been associated with mild to moderate neurologic damage affecting cognitive development.⁴⁵ Elevated serum bilirubin levels are associated with sensory hearing loss in premature infants,¹² and sophisticated neurologic testing has revealed abnormalities in functioning of the acoustic nerve in jaundiced but otherwise healthy infants.^{35,55} Recently, a large collaborative study found an association between peak serum bilirubin levels in premature infants and the prevalence of major neurologic handicaps (primarily cerebral palsy) at 2 years of age.⁵³ Although little argument exists that bilirubin can cause neurologic damage, much debate remains as to what level of bilirubin is potentially toxic. The purpose of this review is not to fuel this debate but rather to explain how phototherapy, the most widely used (and no doubt overused) treatment for neonatal hyperbilirubinemia, employs light energy to pump bilirubin out of an infant's body. A knowledge of how phototherapy works provides a basis for understanding how it can be improved. (This review will not discuss the recent approach of chemoprevention of neonatal hyperbilirubinemia using synthetic analogues of heme to inhibit heme oxygenase.)

STRUCTURE OF BILIRUBIN

The structure of bilirubin, shown in Figure 1, is essentially four pyrrole rings joined by three single carbon bridges. For the middle two pyrrole rings, the bridge is a single bonded, and for the outer two rings, the bridges are double bonds. Each double bond can exist in two different arrangements, or configurations. Such configurations are no longer designated *cis* and *trans*, but are now called *Z* from the German word *zusammen* (together), and *E*, from the German word *entgegen* (opposite). In bilirubin IX α the configurations of these two double bonds are set by the configurations in the parent heme molecule where they are both *Z*. Native bilirubin, shown in Figure 1, is thus 4*Z*,15*Z*-bilirubin IX α .

The structure of bilirubin is shown in a linear fashion in Figure 1, which gives no indication of why the two propionic acid side chains and two lactam functional groups do not make bilirubin water soluble. An explanation is apparent from the three-dimensional structure of

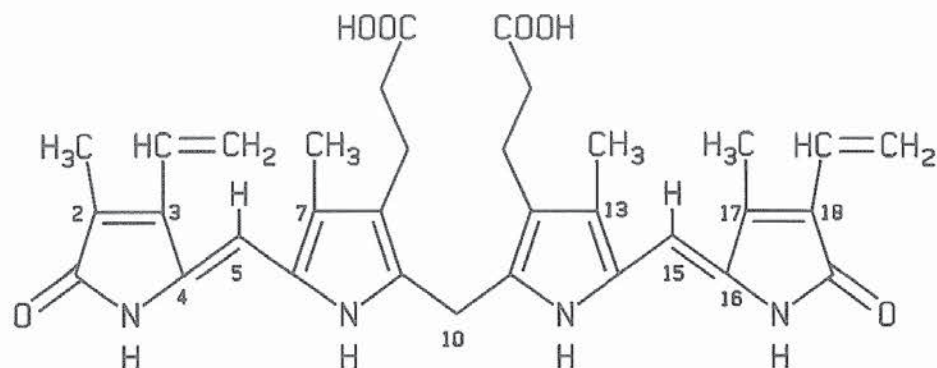


Figure 1. Molecular formula of 4Z,15Z-bilirubin IX α . The carbon atoms are numbered according to standard nomenclature.

4Z,15Z-bilirubin shown in Figure 2.³ Internal hydrogen bonds link all polar groups together, and as a result these polar groups are unavailable for interaction with the solvent, water. Bilirubin's physicochemical properties of hydrophobicity and lipophilicity are the result of its three-dimensional configuration, which depends on the configuration of its two exocyclic double bonds. The resulting ability to pass freely through biologic membranes is beneficial during fetal life, because it allows fetal bilirubin to pass through the placenta for clearance by the mother. After birth, however, this hydrophobicity makes direct excretion in bile or urine impossible and also allows bilirubin to pass through the blood-brain barrier.

Two mechanisms exist to limit the toxicity of bilirubin. Albumin binding provides temporary protection, transporting bilirubin in a high-affinity complex from its site of formation to the liver for final detoxifica-

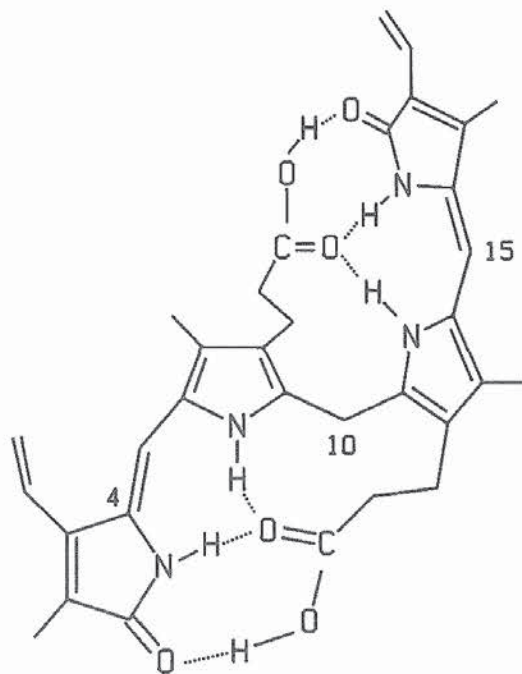


Figure 2. A representation of the three-dimensional structure of 4Z,15Z-bilirubin IX α . Carbon atoms are numbered as in Figure 1. The hydrogen bonds are represented as dotted lines.

tion and elimination.⁶ Hepatic metabolism attaches a molecule of glucuronic acid to one or both of the propionic acid side chains. The water solubility of bilirubin is greatly enhanced by this chemical modification, allowing ready biliary and urinary excretion of bilirubin conjugates. To keep fetal bilirubin from becoming conjugated, which would prevent its passage through the placenta for maternal clearance, hepatic conjugating activity is low and the fetal gastrointestinal tract contains the enzyme β -glucuronidase which hydrolyzes any bilirubin conjugates present. At birth, the hepatic bilirubin conjugation machinery must be turned on and the β -glucuronidase must be turned off. The inability to switch immediately from how bilirubin is eliminated in utero to how it is eliminated ex utero results in the common problem of neonatal jaundice. When this normal delay is coupled with an increased bilirubin load, an alternative mechanism for bilirubin elimination is often required. Turning on a light switch is the most common.

PHOTOCHEMISTRY OF BILIRUBIN

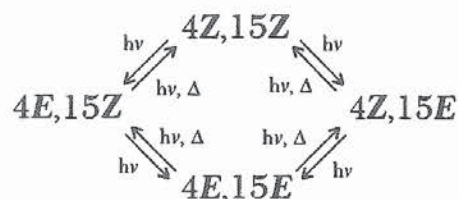
When bilirubin absorbs a photon of light, one of three chemical reactions can occur: photooxidation, configurational isomerization and structural isomerization. Photooxidation forms colorless products and was initially thought to be the process responsible for the elimination of bilirubin in infants. It now appears, however, that photooxidation occurs too slowly to be clinically important. Configurational isomerization is the most rapid reaction, forming an isomer with the *E* rather than *Z* configuration in one of the carbon-carbon double bonds. This was the next reaction believed to be the mechanism of phototherapy; however, the configurational isomers are excreted slowly if at all in jaundiced infants. Structural isomerization is relatively slow, but the product, lumirubin, appears to be excreted fairly efficiently without further modification and to account for most or all of pigment elimination during phototherapy.

Photooxidation

One of the important observations that led to the development of phototherapy was the gradual disappearance of bilirubin from a sample of serum left exposed to sunlight (for a description of the events surrounding the discovery of phototherapy see reference 13). This bleaching phenomenon is the result of photooxidation of bilirubin, which results in the formation of a variety of water-soluble, colorless products.²³ From the beginning of phototherapy in the late 1950s until the early 1980s it was thought that phototherapy worked via the photooxidation of bilirubin. It was not until 1984, however, that photooxidation products were identified unambiguously in the urine of infants undergoing phototherapy.²⁴ Although photooxidation of bilirubin does contribute to the decline in bilirubin during phototherapy, it is a slow process, and all available data suggest that this pathway is a minor contributor to the overall elimination of bilirubin during phototherapy. This relative lack of importance of photooxidation, however, has not yet been proved.

Configurational Isomerization

When native 4Z,15Z-bilirubin absorbs a photon of light, the most likely photochemical reaction is the conversion from double to single bonding of one of the bridges joining the outer pyrrole rings to the middle rings, followed by the rotation of the outer ring by 180 degrees, and the reversion to a double bond.^{26,34,39} This thus alters the arrangement of the chemical groups around the reformed double bond from Z to E. This photochemical reaction does not change the number or type of atoms in the bilirubin molecule but only their arrangement, and so the product is termed a *configurational isomer* of bilirubin. Bilirubin has two double bonds able to isomerize, between carbons 4 and 5, and between carbons 15 and 16 (see Fig. 1). Each double bond can have either the Z or E configuration, resulting in four possible configurational isomers: 4Z,15Z (the native form), 4Z,15E, 4E,15Z and 4E,15E. The E configuration can be reisolomerized back to Z by the absorption of a photon (and also thermally). The total reaction scheme for configurational isomerization of bilirubin can be drawn as follows:



where $h\nu$ represents a photon of light, and Δ represents thermal energy.

If bilirubin is irradiated in a closed system, such as a test tube, the reversibility of the configurational isomerization reactions establishes an equilibrium, and the four different isomers reach steady-state concentrations. When bilirubin is dissolved in organic solvent and irradiated with blue light, the relative steady-state concentrations of the four isomers are: $4Z,15Z > 4Z,15E \approx 4E,15Z \gg 4E,15E$.³⁴

The E isomers of bilirubin are all more water soluble than native 4Z,15Z-bilirubin, because the altered configuration of the double bond disrupts the hydrogen bonding between the propionic acid side chain and the half of the molecule with the E-configuration (Fig. 3).²⁵ The 4E,15E-isomer is the most water soluble, because of the disruption of all of the intramolecular hydrogen bonds, and the 4Z,15E and 4E,15Z-isomers are of intermediate polarity. The E-isomers of bilirubin will spontaneously (in the dark) revert back to the more stable 4Z,15Z configuration, although they are stabilized by binding to albumin. All routine clinical tests of serum bilirubin measure the E-isomers of bilirubin as unconjugated bilirubin, absorbance assays because of the similarity in extinction coefficients, and the van den Burgh diazo reaction because the acidic conditions used rapidly reisolomerize the E-isomers back to the 4Z,15Z form.

Bilirubin bound to human serum albumin shows about a 100-fold preference for configurational isomerization at the double bond between carbons 15 and 16 over the double bond between carbons 4 and 5.^{30,32} Rat or bovine albumin produces no comparable degree of selectiv-

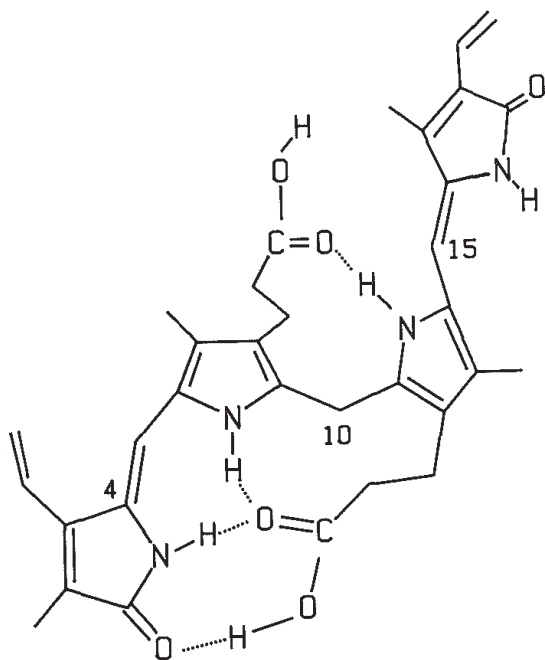
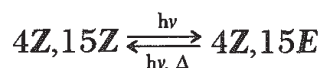


Figure 3. A representation of the three-dimensional structure of 4Z,15E-bilirubin IX α . The hydrogen bonds are represented as dotted lines.

ity. The serum of infants treated with phototherapy contains an overwhelming majority of configurational isomers in the 4Z,15E configuration, indirect evidence that the in vivo photochemistry of bilirubin occurs with the pigment bound to albumin.^{19,36} The selectivity of the isomerization in jaundiced infants reduces the in vivo reaction scheme to:



Again, a steady-state concentration of the two isomers in this simplified scheme will be achieved because of the reversibility of the reaction. The absorption spectra of the two isomers are similar but not identical, and different wavelengths (i.e., colors) of light will produce different rates of the forward and reverse reactions. Thus, the steady-state concentrations of the two isomers are wavelength dependent. Bilirubin bound to human albumin in vitro has 40% of the 4Z,15E-isomer at equilibrium when irradiated with 390 nm (near ultraviolet) light, 32% with 450 nm (blue) light, and only 7% with 510 nm (green) light.^{17,38,42} The steady state amount of the 4Z,15E-isomer is dependent on the wavelength of the light used but is *independent* of intensity. Greater intensity leads to more rapid achievement of the steady-state concentrations but not their amounts. For light containing many wavelengths (e.g., fluorescent lamps), the steady state is determined by the relative emission of the lamps within the bilirubin absorption band.¹⁸ Lamps that appear to the human eye to be the same color, such as the "white" light from Duro-Test Vita Lite (Fair Lawn, NJ). Daylight and tungsten-halogen lamps, in fact, have different distributions of wavelengths, leading to different steady-state amounts of the 4Z,15E-isomer in vitro. In jaundiced infants treated with phototherapy, the color of the lamps also determines the

steady-state concentration of the configurational isomer. The highest serum concentration of the 4Z,15E-isomer is found in infants treated with Special Blue lamps,¹⁰ the lowest in infants treated with green lamps, and intermediate in infants treated with broad-spectrum white lamps.¹⁶ In addition, the intensity (at constant wavelength distribution) does not affect the steady-state concentration of configurational isomer in the serum.⁹ Thus, the 4Z,15E-isomer behaves in jaundiced infants as it does in other closed systems, and although it is formed fastest, it has nowhere to go.

Structural Isomerization

Structural isomerization of bilirubin results in a rearrangement of the atoms in bilirubin. The vinyl group ($-\text{CH}=\text{CH}_2$) attached to the left-most pyrrole ring forms a new bond to the adjacent pyrrole ring, making a new structure with a seven-membered ring (Fig. 4).^{2,32,40} This structure will be referred to as lumirubin here; other names include photobilirubin II, (E,Z)-cyclobilirubin, and unknown pigment. Lumirubin has two chiral centers (carbon atoms to which four different groups are attached), at carbons 2 and 7. Thus, there is not a single lumirubin, but as many as four possible lumirubins. It is not yet known which of the four possible lumirubins is formed in vivo. McDonagh and his co-workers³¹ have demonstrated that lumirubin formed photochemically from bilirubin bound to human albumin is optically active, whereas lumirubin formed from bilirubin dissolved in organic solvents is not optically active. Thus it is likely that lumirubin formed in babies is optically active.

As in the E-isomers, internal hydrogen bonding is disrupted in lumirubin, making it more water soluble than 4Z,15Z-bilirubin (Fig. 4). Lumirubin is also more polar than the 4Z,15E- and 4E,15Z-isomers, and on reversed-phase chromatography, lumirubin has a polarity intermediate between bilirubin mono- and diglucuronides.¹⁴ Lumirubin does not spontaneously revert to native bilirubin, even in the absence of albumin binding, and its photochemical reversion is slow.^{32,40} Lumirubin is measured by clinical assays for serum bilirubin that use absorption, although its extinction coefficient is about 30% lower than that of native bilirubin.²⁹ Lumirubin is not measured in the van den Burgh diazo reaction. The concentration of lumirubin in the serum is generally much lower than that of native bilirubin, however, so that underestimates in clinical assays are of little importance.

The formation of the seven-membered ring that occurs during structural isomerization requires a vinyl group attached to the inside of the outer pyrrole ring, and only the left half of the bilirubin IX α molecule has this arrangement (see Fig. 1). Lumirubin itself can undergo configurational isomerization of the double bond on the right half of the molecule, reversibly forming E-lumirubin (also called [E,E]-cyclobilirubin).

Because lumirubin is formed essentially irreversibly from native bilirubin, in contrast to the configurational isomers, lumirubin does not have a maximum, steady-state concentration. Formation of lumirubin requires both a rotation around the 4,5 carbon-carbon double bond and the formation of a new bond between the vinyl group and carbon 7 of

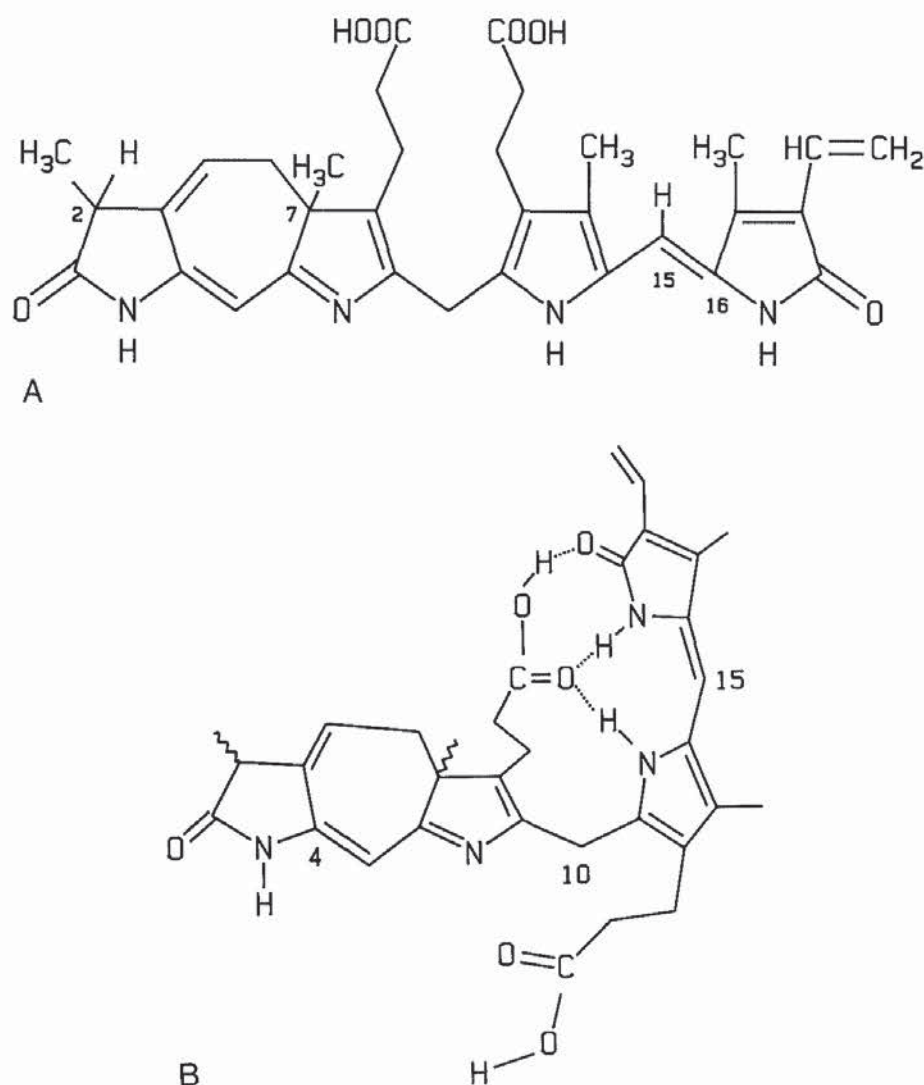


Figure 4. Structure of lumirubin. Linear representation of lumirubin is in A; three-dimensional representation is in B. The hydrogen bonds are represented as dotted lines. Carbon atoms are numbered to correspond to the numbering in the parent bilirubin molecule.

bilirubin (see Figs. 1 and 4). This process could occur as a single step from native 4*Z*,15*Z*-bilirubin or in two steps, with native bilirubin first converted to the 4*E*,15*Z*-isomer and then this intermediate cyclizing to lumirubin.^{4,21} In fact, lumirubin is probably capable of being formed by both the one-step and two-step paths; determining whether a single path dominates under physiologic conditions may be important to understanding ways to increase the rate of lumirubin formation in vivo. Itoh and Onishi²¹ have shown that lumirubin is formed much faster from a mixture enriched in the 4*E*,15*Z*-isomer than from native bilirubin alone, proving that the two-step process does occur. As discussed earlier, however, only small amounts of the 4*E*,15*Z*-isomer (about 1% of total config-

urational isomers) are present when bilirubin is irradiated bound to human albumin. Therefore if the two-step process dominates, the 4*E*,15*Z*-isomer must cyclize to lumirubin extremely efficiently. These same investigators have presented kinetic data to support the rapid cyclization of the 4*E*,15*Z*-isomer to form lumirubin,²¹ and preliminary data on the quantum yield for this process support their conclusion that lumirubin is formed primarily in a two-photon process (Ennever JF, Dressing TJ, unpublished observations). These data suggest the importance of the minor configurational isomer (4*E*,15*Z*), which has generally been ignored in most studies of bilirubin photochemistry.

EXCRETION OF PHOTOPRODUCTS

Elimination of photoproducts from jaundiced infants undergoing phototherapy occurs through urinary and biliary excretion, with biliary excretion likely the major route. Quantitative data concerning the relative importance of urinary and biliary excretion are available only from a study of two patients with Crigler-Najjar type I syndrome.⁷ The patients were infused with radioactively labeled bilirubin and treated with phototherapy. Radioactivity was recovered primarily from feces (72% to 82%) and also from urine (18% to 28%). This study probably overestimated urinary excretion because the infused labeled material likely contained breakdown products of bilirubin that would appear rapidly in the urine. It also should be noted that the two patients were 5 and 7 months old, not newborn infants. However, other evidence also suggests that the major route of bilirubin elimination during phototherapy is biliary excretion.

The relative rates of excretion of configurational and structural isomers of bilirubin have not been measured with accuracy. Lumirubin is believed to be the major photoproduct excreted in newborn infants,^{14,36,37} and the more rapidly formed 4*Z*,15*E*-bilirubin appears to be excreted slowly, if at all. Supporting this conclusion is the much longer half-life in the serum of 4*Z*,15*E*-isomer¹⁵ compared with lumirubin¹⁴ (at least 15 hours versus <2 hours). No measurements have been made of the half-lives of the 4*E*,15*Z* and 4*E*,15*E* configurational isomers, or of *E*-lumirubin. These isomers are present in low or undetectable levels in the serum during phototherapy, and so have been assumed to be unimportant for bilirubin elimination. This assumption may be incorrect.

Additional evidence for the predominance of lumirubin as the route of bilirubin elimination during phototherapy includes the detection of lumirubin as the major bilirubin species in both urine and aspirates of duodenal bile in infants undergoing phototherapy.^{14,22,36} Also, high-intensity phototherapy is more clinically effective and increases the serum concentration of lumirubin, but has no effect on serum concentrations of the configurational isomers.⁹ The different effects on serum concentrations are expected from the basic photochemistry. The formation of the 4*Z*,15*E*-isomer from native bilirubin is photochemically reversible and the maximum concentration is that of the steady state, regardless of light

intensity. No more (and possibly less) than $6 \mu\text{W} \cdot \text{cm}^{-2} \cdot \text{nm}^{-1}$ is necessary to achieve steady-state concentrations in human infants. In contrast, lumirubin is formed essentially irreversibly, so the more intense the light the more lumirubin is formed.⁹ The correlation of higher-intensity phototherapy with an increase in the rate of bilirubin decline and an increase in serum concentrations of lumirubin but not configurational isomers is further evidence that lumirubin rather than configurational isomers is most important in phototherapy. It should be noted, however, that the direct relationship between dose of light and rate of bilirubin decline would also support a major role for photooxidation in phototherapy.

WHICH LIGHT IS BEST?

Next to the nomenclature of the various bilirubin photoproducts, probably nothing is more confusing to the concerned clinician than the conflicting conclusions of countless controlled clinical comparisons of color. Initially blue was "best," then green seemed promising, and now it appears that blue is back. In clinical practice, white has always been the most popular, because no one likes to work around green or blue light.

The reason that color is important is that the first event in phototherapy is a bilirubin molecule absorbing a photon of light. Only light of certain colors (or wavelengths) can be absorbed by bilirubin. Because bilirubin is a yellow pigment, only violet, blue, and some green light can be absorbed. Thus, when infants are treated with broad-spectrum white light, only a fraction of the light is doing anything to the bilirubin. Among the limited colors of light that are absorbed by bilirubin, not all are absorbed equally; the blue light at approximately 450 nm is the most likely to be absorbed, whereas green light is much less likely to be absorbed. Although it is easy to determine which wavelength of light is best absorbed by bilirubin in a test tube, it is not so easy when the bilirubin is in an infant. In an infant, the light must penetrate the skin to reach the bilirubin. The depth to which light penetrates an infant's skin is dependent on the color or wavelength of the light: the longer the wavelength, the deeper the penetration.¹ Thus, green light penetrates better than blue light, which penetrates better than violet light. This phenomenon has the effect of shifting the optimal color for phototherapy from the *in vitro* maximum absorption of bilirubin in the blue toward the blue-green region. Precisely how far this optimal color is shifted is not known. In addition, certain photochemical factors tend to shift the optimal color for phototherapy from the blue region toward the green. These include the shift in the absorption spectrum of bilirubin bound to albumin that accompanies the co-binding of long-chain fatty acids to albumin,²⁸ and the enhanced formation of lumirubin from bilirubin with green light.^{20,29} The end result of all of these factors is that Special Blue (or Super Blue) lamps, which have a spectral output that matches the *in vitro* absorption maximum of bilirubin, do not work as well as one would expect, and that green lights, which have a spectral output that does not match the *in vitro* absorption maximum of bilirubin, work better than one would expect. *In vitro*, the Special Blue lamps produce lumirubin much faster than green

lamps,¹⁸ whereas in clinical comparisons, the results are contradictory, with some studies showing that Special Blue and green are equivalent,⁵⁴ and others showing that Special Blue is better.⁴⁹ The truth is probably that Special Blue light is better than green but not all that much better.

It should be mentioned that all blue lights for phototherapy are not equivalent. In addition to Special Blue (or Super Blue) there are "regular" blue fluorescent lamps. These lamps are *not* narrow spectrum lamps, but actually slightly modified broad-spectrum lamps that have a little more blue and a little less red than white lamps (see emission spectra in reference 18). Many authors fail to make a distinction between the two types of blue lamps, and only those readers who know that Special Blue carry the designation F20T12/BB and regular blue the designation F20T12/B are not misled. Although good data indicate that Special Blue lamps are superior to broad spectrum white light, no data demonstrate that "regular" blue lamps offer any advantage to white light. Because of the penetration factors and the photochemical factors discussed above, the "regular" blue lights *may* not be as good as white light. The widespread use of these "regular" blue lights no doubt stems from the confusion in the literature, in addition to the fact that these lights are considerably less annoying than Special Blue lights. Their use does give the illusion of doing more than just plain white light. It is, however, no more than an illusion.

PROSPECTS FOR IMPROVEMENTS IN PHOTOTHERAPY

Improvement in phototherapy could involve either increased efficacy or safety. Phototherapy has been used on millions of infants worldwide during the past 30 years, and no significant toxicity has been identified. Side effects attributed to phototherapy, including increased insensible water loss, diarrhea, hypocalcemia, riboflavin deficiency, and rashes, are minor and resolve on discontinuing phototherapy. The bronze baby syndrome is a toxicity of phototherapy seen in cholestatic infants inappropriately treated with phototherapy. This effect also resolves, although not immediately after stopping treatment. Visible light, specifically in the 400- to 450-nm (violet and blue) region has been shown to be genotoxic in various *in vitro* systems.^{5,41,44} The amount of potentially genotoxic irradiation received by infants during phototherapy, however, is only a minute fraction of the total genotoxic irradiation an infant receives in his or her first year of life (with the exception of cave dwellers). *In vitro* genotoxicity may not be predictive of human risk.⁵² In addition, the spectral region that is potentially genotoxic does not penetrate the skin more than a millimeter.¹ Thus, the practice of covering the gonads of infants under phototherapy has little scientific basis. It is possible to use only nongenotoxic light (i.e., wavelengths > 450 nm) to treat neonatal jaundice. This could be done, however, only at a cost of decreasing the effectiveness of phototherapy, which as currently administered is certainly suboptimal (*vide infra*).

No real improvement in the delivery of phototherapy has occurred in the three decades since its initial description by Cremer et al.¹¹ Most

investigations have concentrated on comparing lamps of different colors; whereas intensity, a far more important parameter, has generally been ignored. In fact, it is likely that the failure to control or in some cases even adequately measure intensity has led to the contradictory results that have left the clinical practitioner with little useful guidance concerning "which light is best for phototherapy." The only quantitative investigation of intensity was that done by Tan,^{50,51} who found the rate of bilirubin decline to be proportional to light intensity, with the maximum rate at a high dose of phototherapy, more than $40 \mu\text{W} \cdot \text{cm}^{-2} \cdot \text{nm}^{-1}$ in the 425- to 475-nm range. Although Tan's findings were highly significant, no change in the intensity of standard phototherapy has occurred, because of practical limitations in the delivery of the light. Standard phototherapy is administered using eight fluorescent bulbs positioned approximately 50 cm above the infant. The resulting intensity is usually 6 to 12 $\mu\text{W} \cdot \text{cm}^{-2} \cdot \text{nm}^{-1}$ in the 425- to 475-nm range, depending on the age and color of the fluorescent bulbs. (For comparison, light intensity on a sunny summer day [in Cleveland] is approximately $40 \mu\text{W} \cdot \text{cm}^{-2} \cdot \text{nm}^{-1}$ in the 425- to 475-nm range in the shade and $120 \mu\text{W} \cdot \text{cm}^{-2} \cdot \text{nm}^{-1}$ in the 425- to 475-nm range in direct sunlight.) Tan's results and an understanding of the basic photochemistry of bilirubin both suggest that if a method for conveniently delivering phototherapy of much higher intensity were developed, it could provide substantial improvement in the efficacy of phototherapy. Such technology is currently under development (Parker J, Lumitex, Inc., personal communication). It uses a woven fiber optic pad to deliver high-intensity light (as much as $50 \mu\text{W} \cdot \text{cm}^{-2} \cdot \text{nm}^{-1}$ in the 425- to 475-nm region), which has no ultraviolet or infrared irradiation. Because the pad remains cool, the infant can lie directly on the source of light. A device that uses somewhat similar technology, but delivers only the same light intensity as conventional phototherapy, is currently on the market.⁴³

Lumirubin formation is the rate-limiting step in the elimination of bilirubin during phototherapy as currently administered. Higher-intensity phototherapy has the potential for removing the photochemical formation of lumirubin as the rate-determining step. If this proves to be the case, further improvement in phototherapy will depend on enhancing the transport and excretion of lumirubin or other photoproducts. It is clear, however, that as currently administered phototherapy is suboptimal. This is no doubt the result of paying too much attention to color and not enough attention to intensity. The currently used "dose" of phototherapy is based on what is convenient to administer, not on which "dose" is most effective.

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