Volume 1

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Volume 2

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THIRD EDITION

# Textbook of Perinatal Medicine





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CHAPTER

# 2 Neonatal Jaundice

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## INTRODUCTION

Neonatal jaundice is one of the most common conditions of the newborn. Neonatologists are concerned about this problem, not only for the risk of bilirubin encephalopathy in very low birthweight infants and in full-term infants with hemolysis due to different causes [rhesus and ABO hemolytic disease, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, etc.], but also because of the anxiety that jaundice in the full-term neonate gives to parents.

In neonates, jaundice becomes apparent at higher bilirubin serum concentrations in comparison to adults (5–7 mg/dL or 85–120 mmol/L in comparison to 2–3 mg/dL or 35–50 mmol/L). If we take into account clinically evident jaundice, we can say that almost 60–70% of term infants and almost all prematures present with jaundice. But, if we consider a cut-off of > 12.9 mg/dL (220 mmol/L), which in full-term infants is the most accepted limit to consider jaundice as deserving attention, only 5% or less present with a bilirubin serum concentration higher than that.[1,2]

Neonatal jaundice is principally the result of transient deficiency of bilirubin conjugation, some deficiency of hepatic uptake and intracellular transport, and an increased enterohepatic circulation of the pigment. It is notable that bilirubin production in the newborn is two or more times greater than that in the adult per kilogram of body weight.[2] The serum bilirubin level at any point in time is dependent upon the rate of bilirubin production minus the rate of bilirubin excretion.

The largest portion of bilirubin derives from heme breakdown of hemoglobin, myoglobin, mitochondrial and microsomal cytochromes, catalase and peroxidase. Heme degradation probably occurs by auto-oxidation after reduction of ferric ($Fe^{3+}$) heme to the ferrous state ($Fe^{2+}$) by the action of heme oxygenase and NADPH cytochrome c (P450) reductase.[3,4] The methane bridge carbon of the heme is eliminated as carbon monoxide (CO). At the end of this process biliverdin is formed, and is subsequently reduced to bilirubin through the activity of biliverdin reductase. For each molecule of bilirubin formed, a molecule of CO is produced, which constitutes the basis for measuring bilirubin production by determination of the CO concentration in the expired air, or the carboxyhemoglobin content of the blood.[2]

Three isoforms of HO have been isolated, inducible heme oxygenase (HO-1), constitutive heme oxygenase (HO-2), and the more recently discovered and less active heme oxygenase isoform (HO-3).[5] HO-1 is a known stress response protein, whose transcription can be induced by a whole array of stresses, including endotoxin, transition-metals, heme, hemoglobin and other heme proteins.[6] Indeed, it has been suggested that HO-1 induction might represent a generalized response to oxidative stress[5,7,8] and that it could confer cellular protection against oxidant stress. However, recent studies suggest that HO-1 induction might not always be beneficial and that the release of redox-active iron from heme might induce an increase of oxidative stress.[9,10] Moreover, in vitro studies[11,12] suggested that the possible protective antioxidant action of HO-1 could occur within a narrow range, as occurs when HO-1 is over-expressed and free iron release may obviate any cytoprotective effect against oxidative stress.[13]

## BILIRUBIN SOLUBILITY

Bilirubin is derived from heme by separation from methyne-bridge. The configuration on the C-5 and C-14 bridges is very important, and bilirubin preferentially takes the Z form. Moreover, (Z,Z) bilirubin IXa has a configuration that makes the formation of intramolecular hydrogen bridge linkages possible. For this reason, it is almost insoluble in aqueous media (1–10 nmol/L at pH 7.4), but dissolves readily in a number of nonpolar solvents. The degree to which bilirubin (B) ionizes with the propionic acid residue depends on the pH, and this is decisive both for the distribution of the molecule and for its toxicity:

$$B^{2-} + H \leftrightarrow BH^{-}; \; BH^{-} + H+ \rightarrow BH_2$$

The dissociation constants cannot be determined with absolute precision owing to the problem of solubility, but they are found to be approximately $pK_1 = 4.4$ and $pK_2 = 6.5$.[14]

All modifications of the molecule which prevent the formation of hydrogen bridges cause an increase in water solubility. In the human, this takes the form of an esterification of the residue of propionic acid with glucuronic acid, which makes excretion in the bile possible. Obviously, monoconjugated bilirubin is less soluble than diconjugated bilirubin, and can thus precipitate in the biliary tract forming stones. Alkalinization (salt formation) or the addition of nonpolar solvents, such as chloroform, methanol, ethanol, etc. also result in better solubility, and this is the key mechanism used in the laboratory to differentiate between direct-reacting (mostly the conjugated form) and indirect-reacting (unconjugated) bilirubin.

## DISTRIBUTION OF BILIRUBIN IN THE BODY

The distribution of bilirubin in the body is essentially determined by its firm binding to albumin. However, the presence of a visible jaundice seems due, at least in part, to the presence of bilirubin in the skin. Therefore, there is a dynamic competition between tissue binding sites and albumin binding sites. In fact, albumin binds bilirubin according to the law of mass action:

$$\text{Bilirubin} + \text{Albumin} \leftrightarrow \text{Albumin} - \text{Bilirubin}$$

$$\frac{(\text{Albumin} - \text{Bilirubin})}{\text{Albumin} \times \text{Bilirubin}} = KA$$

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Two classes of binding sites have been observed: a primary binding site with an extremely high affinity for bilirubin ($KA_1 = 7 \times 7 \times 10^7$ L/mol at 37°C), and one or two other binding sites with a lesser affinity ($KA_2 = 5 \times 5 \times 10^5$ L/mol). The concentration of free bilirubin is mostly determined by the molar relationship between bilirubin and albumin. However, bilirubin can be displaced from its binding site by certain drugs, such as sulfisoxazole, benzoate, salicylate, etc. Nowadays, every drug intended for use in newborns must be accompanied by evidence that it has no effect on bilirubin-albumin binding.[15]

At the hepatic level, bilirubin is taken up at the sinusoidal membrane level, but about 40% is then regurgitated into the plasma again. The albumin-bilirubin complex seems to bind to specific receptors located on the basolateral surface of the sinusoidal plasmatic membrane of the hepatocyte much better than bilirubin alone.[16] In the hepatocyte, bilirubin reacts with binding proteins, the most important being glutathione S-transferase, thus preventing its regurgitation into the plasma. Bilirubin has a low solubility in water due to the fact that its hydrophilic groups are masked by hydrogen bonds; however, it is made hydrosoluble by esterification in the endoplasmic reticulum, with one or both propionic acid side-chains reacting with a sugar residue to form mono- or diesters; in this way the formation of hydrogen bonds is prevented.[17]

The formation of bilirubin glycosides is catalyzed by uridine diphosphate (UDP) glycosyltransferase, an enzyme system that utilizes bilirubin as an acceptor substrate, and UDP sugars (especially glucuronic acid) that act as donor substrates. Transfer from binding proteins to the enzyme system does not necessarily require a higher affinity for the enzyme binding site, because bilirubin is far more soluble in membranes than in the aqueous cytoplasm, and the reaction could, therefore, take place simply by means of a favorable partitioning. Furthermore, the bilirubin monoglucuronide could be converted into diglucuronide by the same enzyme system, following a 180° rotation of the monoglucuronide molecule, or it could even be excreted without modification in the bile.

## OXIDATIVE STRESS AND NEONATAL HYPERBILIRUBINEMIA

Several reports emphasized the antioxidant role of bilirubin, which in human neonatal plasma seems to have a greater antioxidant potency than urates, α-tochoferol, or ascorbates.[18] In particular, unconjugated bilirubin is able to scavenge singlet oxygen with high efficiency, to react with superoxide anions and peroxyl radicals, and to serve as reducing substrate for peroxidases in the presence of hydrogen peroxide or organic hydroperoxides. Nevertheless, although the antioxidant effect of bilirubin as a scavenger of reactive oxygen species (ROS) is well documented in vitro[19-22] as well as in animal studies,[23] its role in vivo has not been definitively cleared in preterm infants.[22-27]

Recently, two studies investigated the possible relationship between bilirubin plasma levels and oxidative stress in newborn infants[28,29] excluding that bilirubin acts as antioxidant agent "in vivo". It was demonstrated that the decrease of bilirubin plasma level (probably induced by phototherapy) was associated with the concurrent increase of HO-1 activity in blood and the decrease of oxidative stress, suggesting an antioxidant effect of HO-1 exerted "in vivo" by mechanisms other than bilirubin formation. These protective mechanisms could involve the removal of the pro-oxidant heme, the removal of hydrogen superoxide during the degradation of heme, the induction of ferritin synthesis, which sequesters redox-active iron, and the regulation of superoxide anion production. Other possible mechanisms could involve the multiple ways by which CO modulates inflammatory processes, such as the reduction of neutrophil adhesion and extravasation,[30] the reduction of histamine release from mast cells and human basophils,[31,32] inhibition of the expression of proinflammatory cytokines such as TNFα and IL-1β and an increase of anti-inflammatory cytokine IL-10.[33]

These studies confirmed the findings of Yigit et al.[34] who found no correlation between oxidative stress and total bilirubin in preterm infants with nonhemolytic hyperbilirubinemia, and Gopinathan et al.[35] who observed no correlation between bilirubin plasma level and total plasma antioxidant capacity in preterm infants. On the other hand, Belanger et al.[36] found an association between reduction of the antioxidant capacity of plasma after exchange transfusion, and the ensuing decrease of bilirubinemia. This result, however, as indicated by the authors, could be explained by factors other than bilirubin decrease, such as oxidative stress induced by a large amount of transfused blood and the consequent overload of iron through transfusion. Hammerman et al.[37] found a correlation between Btot and plasmatic antioxidant capacity, but the bilirubinemia of their patients was lower than that reported in other studies. To explain these conflicting results, it may be considered that the correlation between bilirubin plasma level and the antioxidant capacity of plasma could change at low and high values, and could be affected by phototherapy through its lowering effect on bilirubin, which, moreover, could also explain the lack of correlation between bilirubin and HO-activity.

## CAUSES OF NEONATAL JAUNDICE

### Physiological Jaundice

So-called physiological or developmental jaundice (which could be especially harmful for the small preterm infant) is due to an imbalance between increased pigment load and reduced hepatic handling. The latter seems mainly determined by the low activity of bilirubin UDP glucuronosyltransferase, the hepatic microsomal enzyme which conjugates bilirubin with one or two sugar moieties. It is now accepted that, even in the absence of impaired biliary secretion, a fraction of the esterified bilirubins formed in the liver normally refluxes from hepatocyte to plasma. Measuring the esterified bilirubins in the plasma of newborn infants has made it possible to demonstrate definitively that neonatal jaundice is mainly due to an increased bilirubin production with subnormal conjugation.[38] On the other hand, infants with the lowest plasma concentration of total bilirubin exhibited the highest fraction of conjugates. The percentage of diconjugates relative to total conjugates is 15% on the first day of life. This value tends to increase slightly with age.[38] In premature infants, serum monoconjugates paralleled the course of total and unconjugated bilirubin, but the values were significantly lower than those found in full-term infants.[17,38]

From the practical point of view, we can rule out the diagnosis of physiological jaundice if plasma or serum bilirubin concentration exceeds at any time 12.9 mg/dL (220 mmol/L) in full-term infants or 5–8 mg/dL (85–138 mmol/L) in preterm infants,[39] if jaundice becomes evident in the first 24 hour of life, if bilirubin concentration increases more than 5 mg/dL (85 mmol/L) per day,

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and if direct reacting plasma bilirubin exceeds 1.5–2 mg/dL (25–35 mmol/L) (it is important to determine conjugated bilirubin by a chromatographic method.[17,38]

## Jaundice in Breastfed Neonates

An increased incidence of early-onset jaundice has been reported in breastfed infants, both full-term and preterm.[40,41] However, an increased bilirubin synthesis, demonstrated by an increased CO production, possibly secondary to caloric deprivation, has not been proven.[42] The process of bilirubin conjugation, investigated in breastfed and formula-fed infants by means of the determination of serum concentrations of unconjugated and esterified bilirubin, and the proportion of diesterified (as percentage of esterified bilirubin) pigment, appeared not to be different between the two groups of infants, showing that bilirubin production and conjugation were not different.[43] In addition, a recent study comparing the incidence of neonatal jaundice in 605 infants exclusively breastfed on demand, in 623 who received both breastfeeding and formula feeding, and in 226 exclusively formula-fed, demonstrates that the incidence of neonatal hyperbilirubinemia (> 12.9 mg/dL or 220 mmol/L) in full-term infants is both insignificant (< 5%) and not correlated with demand breastfeeding.[1] These results were recently confirmed in a population of 2,174 infants with gestational age more than or equal to 37 weeks where hyperbilirubinemia was not found to be correlated with breastfeeding, but rather with an increased weight loss, dehydration, and caloric deprivation which could enhance the enterohepatic circulation of bilirubin.[44]

## Hemolytic Jaundice

Fetomaternal blood group incompatibility, particularly ABO and rhesus hemolytic disease, are the most common causes of severe jaundice. Nowadays, rhesus hemolytic disease is infrequent due to maternal prophylaxis with anti-rhesus immunoglobulins. However, ABO hemolytic disease still remains an important cause of indirect hyperbilirubinemia and anemia in full-term as well as preterm neonates. Suspicion of ABO or rhesus hemolytic disease must be confirmed by a direct Coombs test carried out on the newborn blood.

## Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is frequently associated with neonatal jaundice and sometimes kernicterus. The pathogenesis of this jaundice remains in part unclear, because increased erythrocyte breakdown is not always a major factor in its development.[45] In some patients overt hemolysis, due to different substances, is detected, and in others no signs of hemolysis are detectable (normal level of carboxyhemoglobin). In this group of patients it has been shown that a deficiency in bilirubin conjugation does exist.[45] It is possible that G-6-PD is also involved in some steps (possibly UDP glucuronic acid synthesis) of bilirubin conjugation.

## Congenital Nonobstructive, Nonhemolytic Jaundice

Crigler–Najjar disease is a rare disorder of bilirubin metabolism caused by a deficiency of hepatic UDP glucuronyl transferase, and characterized by high serum levels of unconjugated bilirubin that appear in the first day after birth and continue through life. Based on the responsiveness of the serum bilirubin concentration to phenobarbital, this disease can be distinguished as either type 1, which does not respond to phenobarbital, or type 2, which responds to barbiturates and other drugs that induce enzyme synthesis. Type 2 is probably caused by a partial enzymatic deficiency. In type 1 and type 2 Crigler–Najjar disease, it is possible to detect traces of monoconjugated but not diconjugated bilirubin both in serum and in bile.[46]

# BILIRUBIN ENTRY INTO THE BRAIN

Some clinical observations suggest that several mechanisms may be involved with the entry of bilirubin pigment into the brain. In fact, bilirubin seems to enter into the brain both as free bilirubin acid and as bilirubin-albumin complex, by passage through a disrupted blood-brain barrier that is often caused by hyperosmolality and hypercarbia. It seems that even during physiological jaundice there is a steady passage of unbound bilirubin across this barrier. Furthermore, these low levels of bilirubin do not seem to be harmful; in fact, it is also possible that cerebral stores of bilirubin oxidase are able to metabolize bilirubin in loco. Obviously, the entry of bilirubin into the brain can be significantly increased in the presence of high plasma bilirubin concentrations, particularly if the albumin binding capacity is exceeded.[47] Ahlfors et al. reported that in term newborns unbound bilirubin levels between 0.9 and 2 µg/dL produce subtle and reversible changes in auditory brainstem response latency, and described the case of an infant who developed a kernicterus at a total bilirubin concentration of 31.7 mg/dL and unbound bilirubin concentration of 7.7 µg/dL.[48] However, in preterm infants bilirubin-induced changes in auditory brainstem response can begin at unbound bilirubin level of 0.5 µg/dL and kernicterus becomes likely at 1–1.5 µg/dL.[49]

## Effects of Bilirubin on Neurologic Functions

It is well known that bilirubin acts to uncouple oxidative phosphorylation and, consequently, inhibits the respiratory chain by causing certain toxic effects.[50] However, a number of studies carried out on experimental animals show no difference in bilirubin binding between different brain regions, nor in the rate of bilirubin disappearance from the cerebral tissues.[51] Moreover, it is still unclear as to why bilirubin has a preferential localization at the level of the basal ganglia. One proposed explanation relies on the possibility that bilirubin may be metabolized locally at different rates.[51] In fact, the typical findings of kernicterus are a yellow staining of the subthalamic, dentate and inferior olivary nuclei and the globus pallidus. Cellculture models suggest that bilirubin initially interacts with cellular membranes, affects ion channels and neurotransmitters, and ultimately leads to deranged metabolism and cell death.[52] The clinical picture of kernicterus is also fairly uniform in these children, with convulsions and opisthotonus followed by hypotonia, high-pitched crying and fever. The sequelae in the survivors consist of neurogenic hearing disorders, choreoathetosis with asymmetrical spasticity and paralysis of upward gaze, together with other neurologic manifestations. Ambulation, despite severe athetosis, is generally reached by the age of 5 years.[53]

Brainstem auditory-evoked potentials are altered by bilirubin in various ways.[54,55] In some studies it has been observed to change the conduction latencies, in others it lowered the conduction wave

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amplitude, both of which fit with the follow-up observation of deafness in kernicteric babies. Some studies note reversibility of these altered potentials through lowering of high bilirubin levels.[56,57]

Bilirubin-induced membrane potential-lowering may impair nerve conduction along the auditory pathway, which may be reversible if each cell endures only temporary malfunction or if a sufficient number of neurons in the nerve survive the toxicity to maintain function.

It is commonly accepted that (1) bilirubin may be toxic for cells; (2) kernicterus can occur when unconjugated bilirubin levels are high and (3) the mechanism of bilirubin toxicity is mostly unknown.

## MEASUREMENT OF BILIRUBINEMIA

The majority of published studies on bilirubin in infants were made measuring its level on capillary blood with spectrophotometric methods. Some studies compared capillary and venous measurement of bilirubinemia, but their results were conflicting.[58,59] Therefore, to confirm a high value of bilirubin plasma level in a venous sample is not recommended. Recently, new devices have permitted an easier and more reliable transcutaneous measurement of bilirubin. The Chromatics Colormate III™ (Chromatics Color Science International Inc., New York, NY, USA) is still based on the color of the skin, estimating serum bilirubin from skin-reflectance (skin color) whereas the BiliCheck™ (Respironics, Murrysville, Pennsylvania, USA measures transcutaneous bilirubin by utilizing the entire spectrum of visible light (380 to 760 nm) reflected by the skin. Data obtained using Bili-Check™ suggest that this device provides measurements within 2–3 mg/dL (34–51 µmol/L) of the bilirubin serum concentration.[60] These devices could be used as screening tools but, in some circumstances, also as substitutes for serum bilirubin measurements, in particular when its value is lower than 15 mg/dL (257 µmol/L).

## TREATMENT OF NEONATAL HYPERBILIRUBINEMIA

Bilirubin is bound to albumin in the blood, and when its concentration exceeds the binding capacity of the carrier, unbound or free bilirubin concentration increases and results in its redistribution between the tissues (brain) and the vascular space ('free' bilirubin theory). Thus, not only is the serum bilirubin concentration important in judging whether an infant is at risk of bilirubin toxicity, but the albumin concentration and the bilirubin/albumin ratio are also of critical importance. In fact, Ahlfors suggests that when the bilirubin/albumin ratio is < 8 mg/g (136 mmol/g) and the neonate appears well, exchange transfusion is probably not necessary.[61]

Exchange transfusion, first performed in 1925 by Alfred Purvis Hart and then implemented by LK Diamond in 1947 using the umbilical vein to withdraw and to perfuse blood, was the only treatment available until 1958 when Cremer and colleagues[62] showed that both sunlight and blue light were able to reduce jaundice in newborns. In fact, phototherapy is now the most widely used method worldwide for the treatment of jaundiced babies.

The mechanisms by which light renders the insoluble bilirubin molecule (bilirubin IX-alpha Z,Z), at physiologic pH, soluble and rapidly excretable in the biliary tract are the transformation of the Z,Z configuration at the C4–C5 and C15–C16 double bonds to the E configuration in one or both double bonds, thus forming the configurational isomers E,Z or Z,E or E,E.[63-65] Of these isomers, the predominant one is the Z,E form. However, the Z,E change is reversible, and after phototherapy it reconverts in the bile or in the intestines to the Z,Z isomer. In addition, intramolecular cyclization of bilirubin can occur as a result of phototherapy, to form a structural isomer called lumirubin, which cannot be reconverted to native bilirubin. Moreover, lumirubin, which is formed at a lower rate in comparison to the configurational isomers, seems to be excreted more rapidly in the bile than the other isomers.

There is a striking regional selectivity that causes isomerization to take place at the double bond of the CH-bridges. Because of the specific preference evidenced by one-half of the bilirubin molecule in binding to human albumin, the E configuration in position 15 is the main isomer formed. This selectivity is lacking to a large extent in a number of the animals used in experimental studies. Finally, the available data suggest that bilirubin is bound to albumin at the site of the light effect, namely in the skin.

The extent to which isomerization, cyclization or oxidation exert the therapeutic effect of light is determined mainly by the quantum yield of the photochemical reactions and the speed of the transport processes up to the excretory phase.

The quantum yield of configurational isomerization is probably very high; isomers are formed very quickly, and they can be detected within a few minutes after light treatment. On the other hand, photocyclization proceeds more slowly, and depends on the wavelength employed. Moreover, the quantum yield of bilirubin oxidation is very low, and it is most probable that the excretion of catabolites formed in the process takes place rapidly. Since the excretion rate of lumirubin is very high, it is conceivable that, in phototherapy for neonatal jaundice, bilirubin photocyclization is the most effective mechanism of bilirubin photometabolism, followed by configurational isomerization and, finally, photooxidation.

## THE BRONZE BABY SYNDROME

The bronze baby syndrome (BBS) is a rare pathological condition that appears during phototherapy. The typical characteristic is a grayish-brown discoloration of the skin, serum, and urine. This condition was first described by Kopelman and colleagues,[66] who observed the typical discoloration in the skin of a newborn following phototherapy. They found that the onset of the syndrome was linked to an increase in conjugated bilirubin, implying a cholestatic disorder; moreover, they also related it to hemolytic anemia. Since then, various authors have attempted to explain the biochemical mechanism responsible for the onset of this syndrome.[67,68] In this connection, Kopelman and colleagues noted a reduced bilirubin binding capacity in newborns suffering from BBS. They suspected that bilirubin photoproducts might be responsible both for the bronze discoloration and for the change in binding capacity ascertained by the salicylate method". Autopsy evidence later showed that this peculiar discoloration was also present in the kidneys, liver, and peritoneum. Clark and associates[67] and Rubaltelli and colleagues,[68] in particular, found anatomical signs of kernicterus in two newborns who died with this syndrome. They considered this observation to be confirmation that the pigments responsible for BBS increase the risk of bilirubin neurotoxicity, as suggested by the reported decline in the albumin binding capacity.[66,69]

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In 1982 a notably higher concentration of porphyrins was found in the serum of patients with BBS.[70] Two cases of this syndrome, with very high serum porphyrins, probably due to some degree of cholestasis, were described.[71,72] The porphyrins were identified as $Cu^{2+}$-uroporphyrin, $Cu^{2+}$-coproporphyrin-, and $Cu^{2+}$-protoporphyrin. In fact, the absorption spectrum of serum specimens from infants with BBS showed spectral features typical of bilirubin (peak absorption around 460 nm), as well as an intense band with a peak at about 400 nm and broad absorbance in the near-UV and the 600–700 nm region. The latter two features were not confirmed by the absorption spectra of control sera. The sera of bronze babies also exhibited a wide range of fluorescence emission spectra, with peaks at 585, 619 and 670 nm. This finding indicates that absorption in the 400 nm band does not reflect the presence of residual hemoglobin in the serum because hemoproteins are known to be devoid of any appreciable fluorescence in the red region. Instead, the emission spectra observed are characteristic of porphyrin compounds.

Chromatographic separation led to the conclusion that the main component is $Cu^{+}$-protoporphyrin IX, although small amounts of $Cu^{+}$-coproporphyrin II and $Cu^{+}$-uroporphyrin III are also present. These porphyrins do not seem to have an appreciable photosensitizing effect. Furthermore, there was no evidence of significant alterations in the UV spectrum of irradiated serum from infants with BBS or in cord blood serum with added synthetic $Cu^{+}$-porphyrins. This is due to the well-known shortening of the half-life of excited porphyrin as a consequence of the binding of the $Cu^{+}$ ion on the tetrapyrrolic ring.[73]

These investigations show that the grayish-brown skin color is a result of the photolability of the $Cu^{2+}$porphyrins. Indeed, $Cu^{+}$-porphyrins in the serum of infants with BBS or in aqueous solutions are converted under irradiation with visible light into brown photoproducts with a higher absorption in near-UV and red spectral regions. Moreover, the presence of bilirubin increases the photodegradation rate of $Cu^{+}$-porphyrins, suggesting that bilirubin acts as a photosensitizer in this process.

## GUIDELINES FOR THE TREATMENT OF UNCONJUGATED HYPERBILIRUBINEMIA

### Full-Term Newborn Infants

Neonatal jaundice (total bilirubin serum concentration > 12.9 mg/dL) (220 mmol/L) occurs in around 5% of normal neonates.[1] In the majority of cases, it is a physiologic or developmental jaundice,[1,74] which does not need any treatment. However, it is important to exclude the presence of a rhesus or ABO hemolytic disease, and the possibility that the jaundice could be an early sign of an inborn error of metabolism, or sepsis, etc.

It is suggested that a direct Coombs test plus blood group and rhesus determination should be carried out on the cord blood of every neonate, and, when jaundice is present, the neonatologist should evaluate the appropriateness of a serum bilirubin determination in relation to the day of appearance and intensity of the jaundice, etc. A bilirubin serum level of 20 mg/dL (340 mmol/L) in a normal full-term newborn infant is no longer considered an indication for exchange transfusion.[74] In the absence of a hemolytic disorder, and with a bilirubin level in the range 20–25 mg/dL (340–425 mmol/L) exchange transfusion might be considered, but this decision must be based on a careful evaluation of the risk/benefit ratio.

Following Wennberg's suggestions,[47] one should take into consideration not only the serum bilirubin level but also the albumin serum concentration: that is, by multiplying the albumin value in grams by seven, a value is obtained which corresponds to the level when an exchange transfusion is indicated.

It is recommended that phototherapy be started during the first 24 hour of life if the serum bilirubin level exceeds 4–7 mg/dL (70–120 mmol/L), or during the second 24 hour of life if it exceeds 11–15 mg/dL (190–260 mmol/L), and in all cases whenever it exceeds 15 mg/dL (260 mmol/L). Phototherapy should be carried out for at least 24 hour, and should be interrupted when bilirubin serum concentration is decreased by more than or equal to 2 mg/dL (≥ 35 mmol/L).

However, the American Academy of Pediatrics has recently published guidelines for the management of hyperbilirubinemia in the newborn infant of 35 or more weeks of gestation, which report in depth on current recommendations for prevention, diagnosis, and treatment of neonatal jaundice.[75] The approach to jaundice in preterm infants appears more difficult because there are no specific evidence-based guidelines for the use of phototherapy and exchange transfusion in these infants. Different authors have reported a range of bilirubin plasma level for intervention in various circumstances, but none of these indications has greater validity than another.[39] However, considering that in preterm infants kernicterus has almost disappeared probably due to aggressive phototherapy, it is probable that the current management of jaundice in these infants is correct.

Other possible therapeutic interventions are immunoglobulin therapy in immune hemolytic jaundice and administration of the heme oxygenase inhibitor Sn-mesoporphyrin. Alcock et al., in a metaanalytical study on term and preterm infants with rhesus and ABO incompatibility, found that the rate of exchange transfusion decreased significantly in the immunoglobulin treated group. The mean number of exchange transfusions per infant was also significantly lower in the immunoglobulin treated group.[76] As for Sn-mesoporphyrin, its use is very promising both for the prevention and the treatment of neonatal jaundice. However, this drug is as yet under research and is not commercially available.[77]

### Premature Newborn Infants

In the last few years, a number of studies have shown that currently neither kernicterus nor clinical signs of bilirubin encephalopathy are found in premature babies (see the important review of Conolly and Volpe).[78] These findings were reported despite the fact that higher bilirubin serum concentrations were allowed compared with studies reported in the 1960s and 1970s, when kernicterus was not a rare occurrence.[79,80] It is possible that the improved quality of health care has reduced the appearance of preterm kernicterus, the pathogenesis of which is still not completely understood.[80-85]

The definition of prematurity (< 37 weeks of gestational age) includes neonates of very different gestational ages. Moreover, a generous use of phototherapy has allowed a reduction of high bilirubin serum concentrations, and as a result exchange transfusion ís no longer used very often. However, it seems rational to initiate light treatment independently of the age of the premature infant, whenever the bilirubin serum concentration is more than or equal to 8 mg/dL (135 mmol/L), provided that no hemolysis is present. In fact, exchange transfusion must be considered when bilirubin reaches the level of 18 mg/dL (305 mmol/L). Furthermore, for the

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premature newborn one can use Wennberg's formula[47] to identify infants needing exchange transfusion: multiplying by six the value of serum albumin concentration (in grams) one obtains the threshold value for exchange transfusion.

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