Kernicterus: Past, Present, and Future
Audrey K. Brown

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Kernicterus: Past, Present, and Future

Audrey K. Brown, MD, FAAP*

Early History of Neonatal Jaundice

The concept of a relationship between severe neonatal hyperbilirubinemia and kernicterus evolved slowly. Jaundice was recognized in ancient as well as biblical times as a manifestation of disease. However, according to Louis K. Diamond (Fig. 1), who reviewed the history of neonatal jaundice, (1) the first record concerning jaundice of the newborn appears to be by Barthomomaeus Metlinger in 1473 in his book *Ein Regiment der Jungen Kinder.*

The occurrence of jaundice shortly after birth as well as some suggestions for homeopathic treatment were mentioned by Michael Ettmüller in his 1708 treatise “De Infantum Morbis.” (1) An early description of icterus neonatorum was published in 1742 in London by John Burton in his treatise “A Full View of All the Diseases Incident to Children.” He suggested that “jaundice generally yields to any gentle purgative.” (1) This same approach was used by Condie in 1853 in Philadelphia. (2) At that time, he wrote that icterus neonatorum seemed to be “connected with the want of a free evacuation of meconium.” He suggested the use of castor oil or a small measure of calomel or rhubarb. It is interesting that he noted that the jaundice was known at times to be accompanied by a “good deal of drowsiness.”

There were several publications in France concerning neonatal jaundice in the late eighteenth and early nineteenth centuries, the most significant of which, according to Thor Hansen, (3) was the thesis submitted by Jacques François Hervieux and defended by him for his M.D. degree at the University of Paris in 1847. The thesis was entitled “De l’ictère des nouveau-nes” (On the jaundice of newborns). Thor Hansen, to whom we are grateful for having reviewed the original French thesis, pointed out that the introductory section of the Hervieux thesis contains a valuable review of works by previous authors, including a description of the publication by M. Baume of a “Treatise on icterus or jaundice of newborn infants.” This treatise had been awarded the prize in a competition sponsored by the University of Paris in 1785 for the best work regarding: “Describe neonatal jaundice and distinguish those circumstances in which treatment is needed and those in which we must only await the natural course.” The popularity of this work is evidenced by the fact that the first edition was completely sold out and a slightly revised edition was published in 1806. (3)

Baume’s treatise was based on his observations of about 10 jaundiced infants, the first being his own daughter. These observations prompted him to propose insightful theories about possible causes of neonatal jaundice, including delayed meconium passage and the reabsorption of bile from the duodenum. Baume also described somnolence and poor feeding among infants who had significant neonatal jaundice, which we now recognize as symptoms of bilirubin toxicity.

Another French physician, Billiard, is mentioned in Hervieux’s review. Among the 80 jaundiced cases he had autopsied, Billiard observed yellow color of the brain in just a few. In contrast, Hervieux, who had based his report on observations made on 45 jaundiced infants, 44 of whom he autopsied, described jaundice of the brain in 31 of the 44 autopsied newborns. According to Hansen, although the pattern of staining of the brain described by Hervieux was not homogeneous, it did not seem to conform to that subsequently characterized as kernicterus. (3)(4)

First Descriptions of the Neuropathoanatomic Findings in Kernicterus

Johannes Orth is credited with publication of the first description of the characteristic pathoanatomic findings in kernicterus in 1875. (5) Hansen noted in his historical review
that Orth, while working as an assistant to Virchow in Berlin, described yellow staining in the brain of a jaundiced infant that was most intense in the basal ganglia and hippocampus. The autopsied neonate had been born nonicteric but became jaundiced shortly after birth. Two days after birth she died; extreme jaundice was her only symptom. Although the brain was very yellow, a much more intense staining was found in the basal ganglia, the wall of the third and fourth ventricles, the hippocampus, and central parts of the cerebellum. Orth also noted that although microscopic examination revealed that the neurons of the basal ganglia were stained, the glial cells were not. At autopsy, all the organs of this infant were intensely jaundiced but with an underlying pallor suggestive of anemia. Interestingly, Orth speculated that the intense jaundice in this infant may have had a hematologic cause. (4)

In 1904, Christian Georg Schmorl was the first to use the term kernicterus (nuclear jaundice) to describe the intense yellow staining that he observed in the nuclei of the brains of 6 of 120 jaundiced infants at autopsy. (6) He apparently initially used the term in presenting his observations on the pathoanatomic changes in the brains of jaundiced newborns at a meeting of the German Society for Pathology, which Hansen speculates was held in 1903. (4) He had observed diffuse yellow coloring of the brains in 114 of the 120 jaundiced infants, but only the brains of six infants manifested the more intense staining in the basal ganglia and medulla oblongata. Because of the specific sites of intense yellow staining, he coined the term kernicterus. He credited Orth with having made similar observations. Schmorl also observed that the yellow color in the brain disappeared unless the specimens were preserved in formaldehyde.

Subsequently, the clinical and neurologic correlates of this pathologic finding were described. The term kernicterus came to be applied to the autopsy findings as well as the signature acute clinical constellation and the characteristic long-term neurologic sequelae seen in affected infants.

**Early Descriptions of Severe Neonatal Jaundice and Central Nervous System Findings**

Evans and Polani wrote an excellent review of the early publications relating severe neonatal jaundice and neurologic sequelae. (7) They pointed out that Pfannenstiel is credited with the first clinical description of familial icterus gravis neonatorum in 1908 and that in some countries this syndrome is called Pfannenstiel disease. However, according to these authors, severe neonatal jaundice occurring in families had been described earlier by several physicians, including Ashby in 1884 or 1885. Evans and Polani cited many reports of severe jaundice with neurologic findings occurring in families, such as acute and chronic central nervous system (CNS) signs described in 1902 by Arkwright in one family. One member of the family had died on the third day after abnormal ocular movements and spasticity followed by the development of convulsions. Another member of the same family developed early jaundice that lasted 2 weeks and was followed by anemia. At 1 year of age, a diagnosis of “infantile paralysis” was made when difficulty in standing and walking persisted. Beneke in 1907 described a family in which the fifth pregnancy yielded preterm twins who became jaundiced, developed early clonic and then tonic “spasms” of the limbs and back, and died on the third day after birth. Kernicterus was found when an autopsy was performed on one of them. (7)

In 1905, Auden also described a series of successive fatal cases of severe neonatal jaundice occurring in families. (8) In 1908, Esch was the first to link the clinical findings of acute kernicterus with the characteristic neuropathologic findings of kernicterus at autopsy of an infant who died with severe familial neonatal jaundice. (9)

Despite these early accounts, the relationship between icterus gravis neonatorum and neurologic sequelae was not widely appreciated. Therefore, in 1914, Guthrie’s description of a child who had a history typical for familial icterus gravis neonatorum and displayed hypotonia and choreo-athetosis at 19 months was hailed as the first clinical description of kernicterus. (10) Subsequently, many cases of familial icterus gravis neonatorum with neurologic sequelae were described, but the relationship of these cases to Rh hemolytic disease remained to be discovered.

In 1932, Diamond, Blackfan, and Baty wrote their famous paper “Erythroblastosis fetalis and its association with universal edema of the fetus, icterus gravis neonatorum, and anemia of the newborn.” (11) However, the cause of this syndrome remained obscure.

**The Relationship of Erythroblastosis Fetalis to Rh Isoimmunization Defined**

Levine and Stetson found atypical agglutinins in the blood of the mother of a stillborn fetus in 1939. (12) In their epoch-making paper, they described a severe hemolytic transfusion reaction in the mother that led to their discovery of a new blood group antibody. As Louis Diamond later wrote, Levine’s scientific curiosity and careful analysis of an unusual transfusion reaction led to...
the understanding that icterus gravis neonatorum and erythroblastosis fetalis were due to a previously unknown blood factor. (13) The discovery stimulated interest in the dormant field of blood group serology.

Landsteiner and Wiener in 1940 gave the name “Rhesus” or Rh factor to the factor detected by guinea pig or rabbit sera following injection of Rhesus monkey blood. (14) They found that 85% of human red blood cells gave positive reactions, and in 15% the reaction was negative. Because this was the same proportion found by Levine with his original human antiserum, they also named the human blood factor “Rh.” In 1961 it was found that the two sera were not identical; the animal sera detected a “D-like” antigen in the blood of Rhesus monkeys. (15) However, by then it was impractical to change the name of the human antibody from “anti-Rh” because of the vast literature that had accumulated in the interim.

Evolution of the Management of Rh Erythroblastosis Fetalis

The discovery of the cause of familial icterus gravis neonatorum was followed by an explosion of discoveries related to the detection and treatment of erythroblastosis fetalis. However, treatment was directed for several years at control of hemolysis and anemia rather than at prevention of severe jaundice and kernicterus. A series of reports from Louis Diamond’s service at the Boston Children’s Hospital during the 1940s traces the evolution of thought about treatment of Rh hemolytic disease from the aim of treating anemia to that of preventing kernicterus.

In 1945 and 1946, simple red blood cell transfusions were administered to correct the anemia in infants who had erythroblastosis fetalis. Exchange transfusion then began to be used, a procedure popularized by Wallerstein through his publication in Science in 1946. (16) From 1946 until 1949, single exchange transfusions were used at the Boston Children’s Hospital in an effort to remove antibodies as well as antibody-damaged red blood cells and to correct anemia. (17) From 1949 to 1952, multiple exchange transfusions were given because that practice was found to reduce mortality and the incidence of kernicterus. (18) It was not until 1952 that the association between high serum bilirubin levels and the occurrence of kernicterus was recognized and treatment was recommended based on the serum bilirubin level. David Y.Y. Hsia at the Boston Children’s Hospital showed that kernicterus developed in 18% of infants who had Rh hemolytic disease and serum bilirubin levels between 16 and 30 mg/dL (273.6 and 513 mcmol/L) and in 50% of infants who had levels greater than 30 mg/dL (513 mcmol/L). (19) On the basis of these findings, it was recommended that the serum bilirubin level in Rh hemolytic disease be maintained below 20 mg/dL (342 mcmol/L) by repeated exchange transfusions if necessary. In 1948, Lande published his seminal paper on long-term sequelae in survivors of kernicterus due to Rh sensitization. (20)

Kernicterus Not Restricted to Rh Hemolytic Disease

By 1950, it was recognized that the occurrence of kernicterus was not restricted to infants who had Rh hemolytic disease. In 1950, Wolf Zuelzer (Fig. 2) and Roxie Mudgett analyzed the etiologic basis for the occurrence of 55 autopsied cases of kernicterus. (21) They found two groups of infants who had kernicterus: those who had Rh hemolytic disease (Group I) and those in which that diagnosis was excluded (Group II). Seventy-five percent of infants in Group I were preterm. Other major diagnoses in Group II included sepsis, pneumonia, and diarrhea. In contrast to the early jaundice in infants who had Rh hemolytic disease, the onset of icterus in Group II was delayed. The average survival time in those who had hemolytic disease and developed kernicterus was 3.4 days compared with 7 days in those who did not have Rh hemolytic disease.

Clear-cut clinical symptoms of kernicterus were lacking in the majority of infants in both groups. However, signs of CNS damage occurred more frequently in those without Rh hemolytic disease, presumably because they survived about 3 to 4 days longer than those who died with Rh hemolytic disease. Perhaps the longer survival of the Group II infants allowed more time for development of classic signs, such as opisthotonus and convulsions. It is of interest that about 40% of the infants in Group II who had kernicterus were ABO incompatible. (The paper was published before the description of the clinical syndrome of ABO hemolytic disease in 1954.)

This investigation provided clear evidence that kernicterus could be produced by causative factors other than Rh hemolytic disease. Earlier, many had held that kernicterus did not occur in the absence of erythroblastosis fetalis. (22) However, the role of sepsis in these cases was impossible to delineate with confidence. As Zuelzer pointed out in his discussion in the 1950 publication, an accurate analysis of the causes of kernicterus had not been possible in the pre-Rh era when Schmorl (1904) (6) as well as DeBruyne and van Creveld (1948) (23) had attributed the kernicterus in their cases to sepsis. (The problem is well illustrated in the latter case.
because testing of the maternal sera years later revealed Rh antibodies. (21))

In 1953, John Crigler and Victor Najjar (24) reported the occurrence of kernicterus in congenital hyperbilirubinemia, strengthening the concept that kernicterus was related to hyperbilirubinemia, even in the absence of hemolytic disease. In that same year, A.E. Claireaux identified the yellow pigment in the brains of infants who had kernicterus as bilirubin. (25)

**Serum Bilirubin and Kernicterus in the Preterm Infant**

In 1958, Crosse, Wallis, and Walsh in England reported that during the period of 1945 through 1952, 1.08% of all infants admitted to their premature nursery developed kernicterus and that approximately 70% of these neonates died. (26) They found that 19% of preterm infants who had bilirubin levels of 22 to 27 mg/dL (376.2 to 461.7 mc mol/L) and 33.3% of those who had levels greater than 30 mg/dL (513 mc mol/L) developed kernicterus. They recommended replacement transfusion as a means of preventing kernicterus in preterm infants.

Because both term and preterm infants had been shown to develop hyperbilirubinemia and kernicterus, even in the absence of hemolytic disease, exchange transfusion was proposed for such infants as well as those who had hemolytic disease to keep the serum bilirubin from exceeding 20 mg/dL (342 mc mol/L). There were then, as now, conflicting opinions concerning the appropriate serum bilirubin level, as well as circumstances for which exchange transfusion should be performed. Even during the 1950s, it was recognized that serum bilirubin alone was an insufficient indicator of the risk of kernicterus in an individual infant. Nonetheless, exchange transfusion for hyperbilirubinemia with or without hemolytic disease became the standard of care to prevent kernicterus, and the major criterion for performing an exchange was the serum bilirubin level.

**The Role of Uridine Diphosphate Glucuronosyl Transferase in Neonatal Jaundice**

From 1950 to 1960, several important discoveries were made about bilirubin metabolism. These opened the way to greater understanding of the cause of neonatal jaundice as well as to new approaches to preventing and treating hyperbilirubinemia and preventing kernicterus. A major breakthrough was the demonstration by Rudi Schmid that direct reacting bilirubin was bilirubin glucuronide and that indirect reacting bilirubin was unconjugated. (27) In 1957, Brown demonstrated that the enzymatic system for conjugating bilirubin as a glucuronide gradually developed in late gestation and during the neonatal period. (28) Both bilirubin glucuronosyl transferase and uridine diphosphate glucuronosyl (UDPG) dehydrogenase were found to be poorly developed in the neonate. (29) These inadequacies are the major factors responsible for the development of neonatal jaundice due to unconjugated bilirubin, which occurs in about two thirds of neonates. These investigators also demonstrated that severe hyperbilirubinemia occurred in term infants who did not have Rh or ABO hemolytic disease. (30) Exchange transfusion was recommended for such infants to remove bilirubin. These researchers demonstrated that bilirubin was removed from the extravascular compartment, as well as from the plasma, during exchange transfusion. (31) Because time was required for equilibration between the compartments, rapid exchange transfusion was less efficient than slow transfusion.

**The Role of Albumin Binding of Bilirubin**

In 1956, Silverman and associates reported a higher incidence of kernicterus among preterm infants who received sulfasoxazole compared with those who received oxytetracycline as antibiotic prophylaxis. (32) Harris, Lacey, and MacClean, working in the same institution at that time, happened to be measuring bilirubin levels in preterm infants, including the 43 infants who received sulfasoxazole, nine of whom developed kernicterus. They reported that only one of the nine infants who developed kernicterus had a bilirubin level in excess of 15 mg/dL (256.5 mc mol/L). (33) Clinical signs of acute kernicterus appeared 16 to 42 hours prior to death, and serum bilirubin levels fell prior to death. Neither group of investigators had an explanation for this tragic event until years later, when the influence of sulfasoxazole on albumin binding of bilirubin was elucidated by Odell. (34) He demonstrated that albumin binding was essential for bilirubin to remain in the plasma. Substances such as sulfasoxazole competed for albumin binding sites and displaced bilirubin, allowing greater movement of bilirubin into the tissues and extravascular space. These observations contributed to greater understanding of factors that increased the risk of kernicterus. This is another example of the pursuit of clinical observation leading to an understanding of fundamental features of the development of kernicterus.

**The Toxicity of Bilirubin Demonstrated**

Another major line of investigation concerning kernicterus was inquiry into why bilirubin caused brain
damage. In 1954, Richard Day demonstrated that bilirubin inhibited brain tissue respiration in vivo. (35) In 1956, Rolf Zetterstrom and Lars Ernster showed that bilirubin was an uncoupler of oxidative phosphorylation in mitochondria. (36) In 1959, Johnson and colleagues demonstrated the usefulness of the Gunn rat, which has an inherited deficiency of glucuronosyl transferase and kernicterus, as a model to study factors that increase the risk of brain damage. (37) It became clear that many factors contributed to the risk of kernicterus at a given level of bilirubin. Wolf Zuelzer commented at the time, “The serum level of bilirubin is a very imperfect indicator of the summation of many factors involved in the genesis of kernicterus.” (Personal communication, 1959)

**Phototherapy Begins – 1956**

Another major advance during this period was the discovery that light caused a decrease in jaundice as well as in serum bilirubin both in vivo and in vitro. The story of that fortuitous discovery bears repeating because it emphasizes that observation is still a most important feature in unlocking nature’s secrets. Sister Jean Ward (Fig. 3) at the Rochford General Hospital in Essex, England, was an enthusiast for exposing the infants in her care to sunlight. She observed that sunlight reduced jaundice in the exposed areas of the infants and that the covered (eg, diapered) areas remained jaundiced. She reported this while on rounds, and a young registrar, Dr. Cremer, pursued this observation. (38) He exposed jaundiced infants to sunlight or blue fluorescent light and demonstrated decreased jaundice and levels of serum bilirubin. He had also observed that the level of bilirubin in a test tube decreased when left exposed to light.

Although the mechanism of this transformation was not determined for several years, phototherapy began to be used throughout the world to treat jaundiced infants. In the United States, however, there was skepticism about this new approach until Jerry Lucey (Fig. 4) performed a controlled study in the preterm nursery. (39) A cohort of preterm infants was exposed to fluorescent lights from birth and another cohort, without exposure to the fluorescent lights, served as control infants. This experiment demonstrated that the hyperbilirubinemia of prematurity could be prevented. Following this study, the use of phototherapy to treat hyperbilirubinemia, not only to prevent it, became widely accepted. It was not until 1985 that the safety and efficacy of phototherapy was demonstrated by the National Institute of Child Health and Human Development cooperative controlled trial. (40) This study showed that treatment of infants with phototherapy, at designated levels of bilirubin for each birthweight group, safely reduced the number of exchange transfusions needed to control hyperbilirubinemia and prevent kernicterus.

Freda, Gorman, and Pollack revolutionized the management of erythroblastosis fetalis in 1964 through the development of Rhogam to prevent maternal sensitization to the Rh factor. (41) Although Rhogam did not help those already sensitized, when given according to specific guidelines, it prevented new sensitization and over time markedly reduced the occurrence of Rh erythroblastosis. Interestingly, it was the earlier clinical observation that Rh isoimmunization was unlikely to occur in the presence of ABO incompatibility between mother and infant when fetal red blood cells were destroyed that suggested the Rhogam approach.

**Measurement of Unbound Bilirubin**

Throughout the 1960s and into the 1990s, major areas of investigation continued to be albumin binding of bilirubin, the measurement and significance of free bilirubin, and the relationship between free bilirubin and kernicterus. Several methods for measuring free bilirubin were devised, but few could be applied clinically. Nakamura and Lee achieved a major advance with an enzymatic method to measure unbound, free bilirubin employing peroxidase and glucose oxidase. (42) This later was adapted to a simple, accurate automated system. (43) In clinical trials, it was possible to relate the concentration of free or unbound bilirubin to bilirubin toxicity, as evidenced by characteristic changes in the brainstem auditory evoked response (BAER). A much closer relationship was found between levels of unbound bilirubin and BAER changes than was evident with levels of total serum bilirubin. (44)

**Kernicterus in Small Preterm Infants**

In the 1970s, the combination of advances in management (ie, use of phototherapy and exchange transfusion) to treat, control, or prevent hyperbilirubinemia and the use of Rhogam to prevent Rh erythroblastosis offered the promise of a major reduction in the occurrence of kernicterus. Simultaneous with these advances was an increase in the survival of very small preterm infants because of advances in perinatal care. At that time, the problem of kernicterus became evident at autopsy of very small preterm infants in which clinical signs usually were not detected. This may have been because symptoms in these infants were not attributed to bilirubin encephalopathy but to their other illness because their bilirubin levels were relatively low. There were several reports during this period of kernicterus occurring at low levels.
of bilirubin in this group. (45)(46) The marked increase in kernicterus found at autopsy of preterm infants in one institution (47) occurred during a limited period that corresponded to the time when benzyl alcohol was used to flush vascular lines. Recently, Ahlfors has shown that metabolites of benzyl alcohol, not the parent compound, compete for albumin binding sites. (48) This may account for this one episode of increased incidence of kernicterus. Other instances of kernicterus in very small preterm infants have not been explained, although the incidence has decreased. This is probably due to the better care provided in special neonatal intensive care nurseries. The incidence of kernicterus declined as management of acidosis and respiratory distress in small preterm infants improved.

**G-6-PD Deficiency and Kernicterus**

Kernicterus was and still is being reported in infants who have glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Reports came primarily from Greece and other Mediterranean countries as well as from China and Africa, where a significant proportion of the population carries the gene for G-6-PD deficiency. (49) Reports of kernicterus also came from the United States, with its diverse population that included African-American, Near-Eastern, and Asian-American infants who had G-6-PD deficiency. Apart from these special circumstances, however, kernicterus had virtually disappeared in term infants by the late 1970s and had become rare even among small preterm infants.

**Loss of Concern About Kernicterus**

The widespread use of phototherapy as well as the use of Rhogam in developed countries had so reduced the need for exchange transfusions that by the mid 1980s many young physicians were no longer instructed in the technique. Furthermore, many residents and other young physicians had never seen a case of kernicterus and were not aware of either the early acute signs or even of the pattern of neurologic sequelae or chronic bilirubin encephalopathy. It is not surprising that during this period several articles reflected the concept that bilirubin was not toxic and that hyperbilirubinemia, particularly among otherwise well term newborns, was not associated with the risk of kernicterus. (50)(51)(52) There developed a general loss of concern about jaundice and hyperbilirubinemia that was reflected not only in the literature, but in new, more relaxed guidelines for the management of hyperbilirubinemia from the American Academy of Pediatrics. (53) This loss of concern had a significant impact because it appeared in conjunction with other changes in newborn care. (54)

In the 1980s and 1990s, three other major changes affected the care of the newborn. First, breastfeeding became predominant and favored over formula feeding. Although it was known that breastfed infants had slightly higher bilirubin levels, this was not a major problem if the frequency of feeding was at least seven times each 24-hour period. Specific lactation counseling was needed to assure adequate breastfeeding. This counseling was often precluded by the second change that occurred, that is, significantly shortened hospital and nursery stay for newborns and their mothers in the United States. During the 1980s and 1990s, the average stay was reduced to fewer than 48 hours; in many instances, infants were discharged from the hospital at 24 or fewer hours after birth. This meant that almost all infants were discharged from the nursery while bilirubin levels were still rising and that there was little time for parental instruction concerning jaundice or feeding. The third change, managed care, emphasized reduction of the cost of medical care, which affected decisions about length of nursery stay and the need for laboratory tests to investigate inappropriate degrees of jaundice.

**The Re-emergence of Kernicterus**

The aforementioned changes in attitude and care were associated with a re-emergence of kernicterus among term and near-term infants, almost all of whom were breastfed and discharged from the nursery within 48 hours without early follow-up. (54)

By 1996, Brown and Johnson reported 42 cases of kernicterus among infants who had been born between 1984 and 1996 (most were born after 1990). (54) Of these cases, 21 had been reported in the literature; the additional 21 cases had been referred directly to the attention of Lois Johnson and myself for medical or legal consultation. Because of this experience, we initiated a pilot registry for cases of kernicterus, asking colleagues to share specific information about their cases. The infants, physicians, and hospitals were not identified by name. By 1999, we had identified 84 cases from 25 of the states in the United States, and those data were presented in part at the 1999 meeting of the American Academy of Pediatrics. (55) More than 80% of the infants who had kernicterus were born after 1990. As expected, 67% of the infants were male and 36% were near-term. It became evident from analysis of the data that loss of concern about hyperbilirubinemia, early discharge from the nursery, and inadequate breastfeeding and dehydration played roles in the recent re-emergence of kernicterus. In
addition, many near-term infants were discharged as though they were term infants. Clinicians failed to recognize that infants of 37 weeks’ gestation, as well as those younger than 37 weeks, are particularly susceptible to the toxic effects of bilirubin. Aggressive treatment of severe hyperbilirubinemia often was delayed, reflecting a failure to realize the significance of prolonged exposure to bilirubin.

The trend can be reversed with renewed concern about hyperbilirubinemia and the potential for kernicterus. Parental education about proper breastfeeding and specific instruction concerning appraisal of jaundice are essential, as is early follow-up and professional evaluation of infants within 2 days of discharge. Physicians should also become aware that early aggressive treatment of severe hyperbilirubinemia is essential to prevent kernicterus or at least to minimize CNS damage. It is hoped that reporting of the reemergence of kernicterus will increase awareness that vigilance and concern about the danger of severe hyperbilirubinemia is needed to prevent the unnecessary tragedy of kernicterus.

A Look Toward the Future

Investigative efforts continue to result in new methods to control or prevent hyperbilirubinemia. Phototherapy has become more intensive, and metalloporphyrins have been used to block the formation of bilirubin through inhibition of heme oxygenase. (56) Newer means have been employed to identify infants at risk, including BAER. Simplified means of determining the presence of increased red blood cell degradation through measurement of end tidal carbon monoxide also promises to identify infants at special risk. (57) Magnetic resonance imaging has permitted identification of areas of the brain damaged by bilirubin. (58) At a time when infants are discharged early and investigation of jaundice is discouraged because of monetary concerns, handheld devices for rapid, noninvasive determination of bilirubin (59) are welcomed as aids for identifying infants at risk in the hospital, office, or even when used in the home by a visiting nurse.

In addition to these newer clinical means of identifying and treating hyperbilirubinemia, advances are being made in the biomolecular and genetic arenas. It has been recognized for many years that neonatal bilirubin levels and the likelihood of hyperbilirubinemia vary among racial and ethnic groups. Recent reports show that genetic polymorphisms in the gene for UDPG transferase as well as missense mutations may account for these differences. (60) This new information should raise awareness concerning groups of infants who have special susceptibility for hyperbilirubinemia. The new genetic information also holds the promise of new approaches to management of those who have inherited deficiencies of bilirubin UDPG transferase.

With renewed concern about infants who have jaundice and application of all that is known about factors that increase the risk of kernicterus, this disorder can be eradicated from neonatal nurseries.

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