A Tale of Two Hospitals: The Evolution of Phototherapy Treatment for Neonatal Jaundice

Phototherapy was developed in the late 1950s and is today considered the mainstay of managing neonatal jaundice. Yet prominent academic leaders continued to promote the older approach of exchange transfusion well into the 1970s, despite the considerable risks involved. This article explores why phototherapy took so long to be embraced, and how pediatric residents were caught in the middle of the controversy.

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The chief rationale of treating newborn jaundice is the prevention of kernicterus, a devastating and often fatal outcome attributed to bilirubin’s effects on the basal ganglia. Infants so affected commonly develop a characteristic choreoathetoid form of cerebral palsy accompanied by severe intellectual disability.1

In the mid-20th century, pediatric researchers scored a breakthrough by demonstrating the efficacy of exchange transfusion in preventing this devastating syndrome. The majority of infants thus treated were Rhesus factor positive (Rh+) children born to Rh− mothers exposed to the Rh factor during a previous pregnancy. Maternal antibodies to neonatal red blood cells caused extensive hemolysis, causing the total bilirubin level to rise rapidly and overwhelm the liver’s ability to process and excrete it. Exchange transfusion, rarely performed today, was a challenging procedure that might keep physicians up all night, patiently withdrawing the infant’s blood through an umbilical venous catheter in small increments by syringe and replacing them with an equal volume of donor blood. The procedure was technically difficult and fraught with the possibility of a fatal electrolyte or fluid imbalance.2

In the late 1950s, phototherapy emerged as another potential treatment of jaundice. In 1956 at Rochford General Hospital in Essex, England, Sister J. Ward noted that sunshine decreased neonatal jaundice. Meanwhile, hospital biochemists noted erroneously low bilirubin levels in samples sitting in sunlight before processing.3 Soon afterward came the first evidence for light as an effective therapy for infantile hyperbilirubinemia.4 A decade later the landmark randomized controlled trial showing the efficacy of phototherapy was published by Pediatrics editor Jerold Lucey in 1968.5 Yet Dr Lucey would later recall that he “spent the next ten years” defending his trial (J. Lucey, MD, personal communication, 2012). To begin with, the epidemiology of jaundice was changing. The advent and implementation of Rhogam therapy in 1968 led to the virtual elimination of kernicterus due to Rh incompatibility, the clinical problem that had chiefly driven the rise of exchange transfusion. Attention was shifting to the management of neonatal jaundice among term infants with ABO hemolysis and those born prematurely. It was unclear whether the numeric thresholds for total bilirubin in Rh incompatibility applied to these patients. Moreover, while investigators generally accepted that phototherapy lowered total serum bilirubin (TSB) levels, many questioned whether TSB actually caused kernicterus or was merely correlated with it. Some raised the possibility that the metabolites of bilirubin might cause kernicterus, including those generated by phototherapy. Many believed “free” bilirubin to be the true cause of brain injury. Most unconjugated bilirubin is bound to albumin; it is only the unbound component that...
can cross the blood-brain barrier and lead to neurologic injury. Although free bilirubin is too unstable to measure directly, new procedures were developed that attempted to estimate it indirectly.\textsuperscript{1,2} US pediatricians divided into 2 camps, with the proponents of phototherapy generally focusing on TSB as the key risk factor for kernicterus and advocates of exchange transfusion arguing that this confidence was misplaced and that phototherapy might well create toxic metabolites of its own. Dr Lucey, who good-humoredly styled himself the “Prince of Light,” was the most outspoken supporter of the benefits of phototherapy, in contrast to his chief adversary, the “Prince of Dark,” Gerald Odell at Johns Hopkins (J. Lucey, MD, personal communication, 2012). Dr Odell promoted the salicylate displacement test as a way to approximate free bilirubin by evaluating the availability of binding sites on albumin.\textsuperscript{6} He argued that if the test revealed no remaining available sites to bind bilirubin, there could be kernicterus risk regardless of how low the bilirubin level was. Alternatively, the presence of available sites implied no risk for kernicterus even with a very elevated TSB. The salicylate displacement test was one of many attempting to identify the amount of dangerous “free” bilirubin.\textsuperscript{7}

Pediatric residents could be caught in the middle, as demonstrated by the example of those who worked in New York City’s Bellevue/University Hospital program.\textsuperscript{8} Sanford Cohen, the head of neonatology at Bellevue and a disciple of Dr Odell’s, promoted the Prince of Dark’s paradigm. The Bellevue NICU had no phototherapy treatment and distrusted TSB; its attending physicians relied on the salicylate displacement test as the primary exchange transfusion criterion. In contrast, jaundiced but otherwise healthy infants were treated with phototherapy (relying on TSB) when managed by general pediatrics on Bellevue’s lower-acuity floor; as were newborns at University Hospital (since renamed Tisch), which had no NICU. Jaundiced but otherwise healthy babies in these settings were treated with phototherapy, whereas those judged to be “sick” were transferred to Bellevue.

The senior resident effectively became gatekeeper, leading infants down the path of either salicylate displacement testing and likely exchange transfusion or TSB measurement and usually phototherapy alone. This created an ethical dilemma for the third-year residents; was the observation and phototherapy route better aligned with a physician’s commitment to nonmaleficence, or simply a means to avoid exchange transfusion, a cumbersome and time-intensive process? This situation continued until an index case in the mid-1970s. A child treated in the Bellevue NICU had an extremely high TSB (well over 20) but “ample sites” by salicylate displacement. As per protocol, he was not treated. The infant soon developed seizure-like activity, an early manifestation of kernicterus. After this, the 6 senior residents decided to change protocol unofficially; for any TSB >20, they would perform exchange transfusion regardless of salicylate binding results. To appease the NICU mandate, they continued to perform exchange transfusions in cases of low TSB but saturated albumin sites. In time, quality assurance tests revealed the poor reproducibility of salicylate displacement. Bellevue stopped doing the test but for years remained partial to exchange transfusion over phototherapy. Although phototherapy has become the standard of care for jaundiced neonates, exchange transfusion remains the definitive treatment of those rare patients who fail phototherapy. Failure of phototherapy, however, is poorly defined. In the 1980s, many suggested exchange transfusion when TSB surpassed 20, drawing from findings of Rh-incompatible neonates with hypoxic insult and fetal hydrops resulting in death. Autopsy revealed basal ganglia staining with bilirubin only in those infants with levels >20. It is difficult to know if these cases from the pre-Rhogam era are relevant to today’s cases of extreme prematurity, racial predisposition, and rare genetic defects.\textsuperscript{1} Current practice supports considerably more conservative use of exchange transfusion. For example, a full-term healthy neonate with hyperbilirubinemia above threshold (set at ~25) is admitted to the NICU to prepare for exchange transfusion and immediately started on phototherapy. Before the procedure, TSB is again tested; if <25, exchange transfusion is deferred and bilirubin levels followed closely. Most of today’s neonatology fellows will never perform an exchange transfusion.\textsuperscript{2}

Finally, the importance and potential clinical utility of “free” bilirubin remain unresolved. Prince of Light Dr Lucey has always felt that “people were wasting their time on that binding” (J. Lucey, MD, personal communication, 2012) because of his personal experience in the laboratory, but many experts disagree. Clinicians use TSB with the now-ubiquitous Bhutani curves\textsuperscript{8} because they work well at avoiding devastating disease, not because of great theory or rigorous clinical testing. From what we know about pharmacokinetics, pharmacodynamics, and the blood-brain barrier, a good measure of “free” bilirubin should be more important than TSB,\textsuperscript{1} but a clinically useful “free”

\textsuperscript{1}Animal models have suggested that hyperbilirubinemia is necessary but perhaps not sufficient for kernicterus, that some disruption of blood-brain barrier may be required.\textsuperscript{10–12}
measurement remains elusive, and the pathophysiology of neonatal bilirubin-induced brain injury remains highly theoretical.

Current American Academy of Pediatrics guidelines recommend that if exchange transfusion is being considered, albumin should be measured to determine a bilirubin/albumin ratio as a surrogate measure of “free” bilirubin and potential danger of kernicterus; promoting the bilirubin/albumin ratio is based on expert opinion only with “limited and conflicting” clinical usefulness. This story from 40 years ago reveals that inductive logic does not always lead to correct clinical decisions and that the best therapy may be poorly understood. There are implications regarding clinical practice, how physician-scientists formulate their questions, which projects merit research dollars, and even how physicians approach alternative medicine. Today’s standard of care is firmly with the use of TSB to stratify risk.

The Prince of Light has won the battle; only time will tell who wins the war.

ACKNOWLEDGMENTS
We thank Dr Jerold Lucey for his discussions on these topics and for being interviewed regarding his role in this story; Dr William Borkowsky for his insight into this period at Bellevue; Dr Martha Caprio for her comments on current practices at these NICUs; and Dr Benard Dreyer for his support on early drafts.

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A Tale of Two Hospitals: The Evolution of Phototherapy Treatment for Neonatal Jaundice
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Pediatrics 2013;131;1032; originally published online May 6, 2013; DOI: 10.1542/peds.2012-3651

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*Pediatrics* 2013;131:1032; originally published online May 6, 2013;
DOI: 10.1542/peds.2012-3651

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