

Preface

Kernicterus (bilirubin encephalopathy) is a highly interesting example of metabolic encephalopathy. It fills all the characteristics of a metabolic encephalopathy in that it can develop rapidly, produces signature signs and symptoms, and is amenable to successful treatment. In the absence of treatment kernicterus can produce irreversible damage, devastating sequelae, and death.

The present volume will examine the history, biochemistry, and physiology of bilirubin, as well as its hepatic metabolism and renal excretion. Chapters will elaborate on bodily disposition of bilirubin and its neuropathology. Both early treatments and current therapy will be discussed in detail. Phototherapy will be presented, and its efficacy and influence on incidence thoroughly examined. New concepts relating to the way in which bilirubin is toxic, and damage to the acoustic system will be examined in detail. The promising treatment using gene therapy will be discussed. This therapy has been successfully used in Gunn rats.

When red blood cells break down, the resulting components include heme and globin. Bilirubin is contained in the heme moiety. The life span of red blood cells is about 120 days in adults, and about 90 days in the newborn. In utero, this significant amount of bilirubin is transferred across the placenta to be excreted by the maternal liver. At birth, the newborn liver is faced with increasing levels of bilirubin, and hepatic capacity for conjugation and excretion have yet to be “tested.” It is not surprising that 20% (or more) of newborn children develop a transient physiological jaundice as the enzymatic machinery becomes functional.

Bilirubin travels in plasma bound to albumin. When taken up by the liver, bilirubin is transformed from lipid soluble to water soluble, facilitating excretion into the biliary system. When bound to albumin, or conjugated with glucuronic acid, bilirubin cannot enter the brain. In the “free” state, lipid soluble bilirubin can enter cerebral tissue, causing brain damage. Why bilirubin enters selective cerebral areas is a fascinating and unanswered question.

Many animal models of kernicterus have been used, but one stands out. A Wistar rat mutant described by C. K. Gunn had a genetic deficiency of the liver bilirubin-conjugating enzyme glucuronyl transferase. This defect correlates with the human inborn error, the Crigler–Najjar syndrome. This exciting finding permitted investigators to study a nearly perfect animal model of kernicterus. The Gunn rat model permitted studies on energy metabolism in neurologically-compromised animals,

and defects in ATP metabolism were, not surprisingly, found. Early *in vitro* studies predicted these definitive results in that they showed conclusively that bilirubin uncoupled oxidative phosphorylation. Electron microscopy reinforced these findings, showing selective changes in cerebellar Purkinje cells and their mitochondria. More refined studies directly measuring ATP in nanogram layers of Purkinje cell-rich layers of the cerebellum of symptomatic Gunn rats showed similar effects on energy metabolites, but not in adjacent molecular and granular cell layers (Reynolds, S., and Blass, J. 1976).

Early neuropathological studies in humans noted the selective anatomical staining. The underlying cause of human kernicterus is frequently erythro-blastosis foetalis, or a deficiency of the liver bilirubin conjugation system. Human brains of kernicteric infants often show yellow staining in the basal ganglia, cerebellum, and brainstem. The focal staining is marked when the patient dies during the acute phase; if the patient dies later, the staining has largely vanished. Before phototherapy, many cerebral palsy patients were the result of hyperbilirubinemia.

One long-standing treatment for newborn jaundice is phototherapy. The benefits of light for ameliorating jaundice were serendipitously discovered by a pediatric nurse who noticed jaundiced newborns experienced fading of the yellow skin pigmentation when exposed to sunlight. Further studies on this important observation showed that phototherapy decreased serum unconjugated serum bilirubin levels. Widespread use of this therapy in the USA lagged behind its use in Europe. Bilirubin is structurally similar to the pigment phycobilin, which captures light energy, and so bilirubin is isomerized into compounds which are water soluble, not toxic, and easily excreted.

The wavelength of light used during phototherapy impacts the extent of bilirubin isomerization. Various studies have demonstrated that turquoise light (490 nm peak with 65 nm spectral width) is considered more effective than blue light (452 nm peak with 55 nm spectral width). Side effects to phototherapy are minor, and include epidermal cell death, ultraviolet light burn, and headaches and vertigo in hospital staff. Because of the limited side effects and strong benefits, phototherapy has continued as an effective treatment for hyperbilirubinemia in the newborn.

The present volume is designed to examine the biochemistry and physiology of bilirubin. Its formation, metabolism, transport, and excretion will be examined in detail. Moreover, the deposition of unconjugated bilirubin into highly specific newborn brain regions will be described in terms of mechanisms. Treatment modalities before and after bilirubin stains brain regions will be considered. The very important concept that kernicterus can cause subtle changes in mentation and behavior will be examined. This area of sequelae to mild degrees of bilirubin entry into brain tissue is critical and largely overlooked. Chapters detailing hyperbilirubinemia in older patients and examining albumin and blood transfusion treatment paradigms are included.

Kernicterus is an excellent example of a metabolic encephalopathy. It clearly produces a biochemical lesion early when the pigment first enters the brain. If initial staining can be minimized, or reversed, permanent damage can be reduced to a minimum. This takes strict attention to detail, and a keen ability for timely diagnosis.

The realization that the early diagnosis of any disorder which might have a biochemical (metabolic) basis has the potential for rapid reversal/improvement, if not outright cure, argues strongly for increased awareness by all health care workers. Kernicterus has a potential advantage in that hyperbilirubinemia usually appears in the newborn nursery when it can be recognized by nurses and by physicians. Another huge advantage for the study of kernicterus is the availability of the Gunn rat model. Hyperbilirubinemia and resultant kernicterus is quite another issue in Third World countries. These world health concerns are of such importance that they constitute the first chapter in this volume.

Chicago, Illinois

David W. McCandless



<http://www.springer.com/978-1-4419-6554-7>

Kernicterus

McCandless, D.W.

2011, XIV, 286 p., Hardcover

ISBN: 978-1-4419-6554-7

A product of Humana Press