

History of Bilirubin

The history of bilirubin actually goes back many hundreds of years, when newborn infants were observed to be jaundiced. More recent accounts of jaundice in newborns seems to have begun in the late eighteenth century. One of those was written by Jean Baptiste Thimotee Baumes (Baumes, J. 1806). This description was published as a chapter in a book entitled *Traite de L'amaigrissement des enfans*. The chapter relating to jaundice is entitled *Traite de L'ictere ou jaunisse des enfans de naissance*.

Before describing the Baumes chapter on jaundice and other historical landmarks relating to jaundice, a recent excellent review of the pioneers in the study of neonatal jaundice and kernicterus has been published (Hansen, T. 2002). Dr. Hansen has provided very interesting and thorough descriptions of early investigators of jaundice and kernicterus. In some cases, he has obtained information from still living grandchildren of these pioneers (Orth). Information in the Hansen manuscript cannot be found anywhere else, and the reader is referred to this outstanding paper on bilirubin history found in any other source, and the book in which resides a chapter on jaundice by Baumes is interesting in its own right. The second edition of the jaundice chapter was published in 1806, and is reproduced in a book of a collection of chapters on the maladies of infants. Other chapters in this book in which Baumes' paper on jaundice appears also include chapters on pneumonia, angina, gangrene, edema, etc.

The Baumes paper is 72 pages in length, and he is listed as a professor of pathology at the School of Medicine at Montpellier, and a member of many medical societies, so he must have been a much respected physician. The copy I have is the second edition, which Hansen says is not as clearly presented as the first edition.

Baumes work was based primarily on a description of ten newborn infants who exhibited jaundice. Baumes makes reference to the liver, so an association between the two was already known. Baumes also describes somnolence and poor feeding, symptoms of cerebral involvement in some of the patients he describes. In all cases, Baumes mentions meconium as having importance. He thought that a delay in passage of meconium might be associated with, or the cause of neonatal jaundice. The idea that meconium retention was prevalent at least as early as the 1850s, when Condie (Condie, D. 1853) stated that newborn jaundice was related to failure of free release of meconium.

Baumes also believed that maternal breast milk, and especially colostrums were beneficial to the correction of neonatal jaundice. The very first observation of Baumes was of his own jaundiced daughter, and one wonders if this fueled his interest in neonatal jaundice. The second edition of Baumes work is in a book, "*Meladies des Enfants*" and as stated above has other chapters, some dated as late as 1841. It would seem that advances in the jaundice field moved at a somewhat slower rate than today.

In his splendid review of the early pioneers in jaundice, Hansen states that Jaques F. E. Hervieux was a critic of Baumes. Hervieux states that Baumes' ideas on the involvement of delayed passage of meconium were "without doubt ingenious, but nevertheless only an intellectual theory." He also states that "Baumes supports his opinion with a very small number of observations, and then concludes with astonishing ease to the great majority of cases."

The first description of bilirubin staining of the brain of kernicteric newborn children is credited to Johannes Orth (Orth, J. 1875). Orth reported on the presence of yellow and red pigments and crystals in the organs of newborn infants. He presented data on 37 newborns, all of whom had evidence of pigment in their kidneys, and "most" others had small amounts of yellow pigment in all other organs. In one severe case who died only 2 days after birth, the brain was yellow, but more intense staining was noted in specific brain regions including the basal ganglia, hippocampus, cerebellum, and walls of the third and fourth ventricles. Examination of the brain microscopically by Orth, revealed that neurons in the basal ganglia contained yellow pigment whereas the surrounding glial components were not stained. This patient's skin was severely jaundiced, yet a pallor was detected, leading Orth to state that the jaundice might have had a hematologic cause. Orth was an assistant to the great pathologist Virchow in Berlin when these observations were made.

Christian Schmorl in Dresden was the first to coin the term "Kernicterus." Schmorl was chief of pathology at the University of Dresden, Medical Faculty. In the Schmorl paper (Schmorl, C. 1904), 120 jaundiced newborn infants who died were autopsied. Of these, most (114) were described as having brain icterus of a diffuse yellow nature with "fat bodies" observed in some cases. The others (six) had "core icterus" in which only particular parts of the brains were yellow. These were mostly in "central ganglia" – basal ganglia, and in the "elongated ganglia" – medulla oblongata. Microscopic study of these brains showed that the yellow pigment was selectively present in neurons in nuclei.

Schmorl also noted an absence of staining in the glial component of these nuclei. It is due to the more intense staining of nuclei in the brains of newborn infants dying from jaundice that Schmorl coined the term "kernicterus" (see Fig. 1). Schmorl correctly credited Orth with publishing similar findings on intra cerebral staining by the yellow pigment.

Schmorl may have also been the first to note that the yellow pigment in brain disappeared over time unless the tissue was preserved in formalin (see Schmorl, Fig. 1).

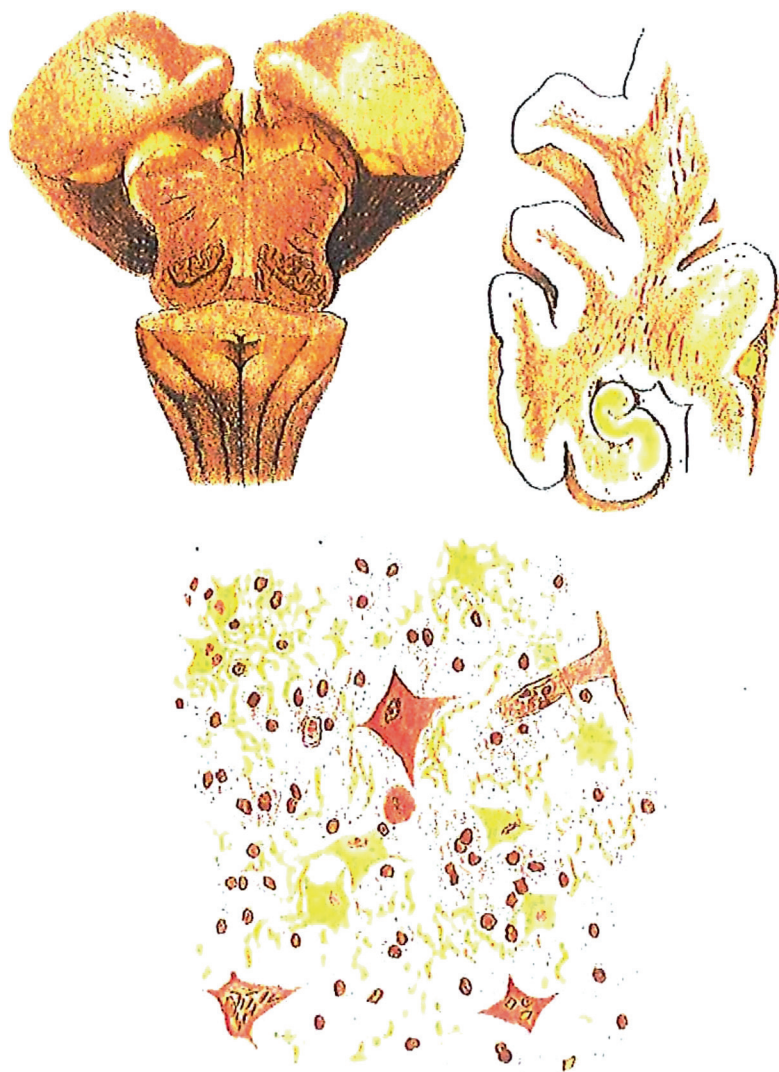


Fig. 1 Figures from Schmoll's early paper showing pigment staining in the hippocampus. These observations resulted in the term kernicterus

The concept evolved that neonatal jaundice could occur in families, and came to be called familial icterus gravis neonatorum. The understanding of the possible familial nature of jaundice was reported by several physicians, including Auden (Auden, G. 1905) and others. Interestingly, Hermann J. Pfannenstiel published a paper in 1908 (Pfannenstiel, H.J. 1908) describing a newborn case of familial icterus gravis neonatorum. This paper has been identified as the first of its kind, although

several similar papers preceded it (see above). The outcome of this is that familial icterus gravis neonatorum has come to be called Pfannenstiel's disease in some quarters.

At this time, (early 1900s) many authors published cases of multiple examples of jaundice and kernicterus in single families. Arkwright (Arkwright, J.A. 1910), for example, reported a family which had 15 children, in which 14 were jaundiced and only 4 survived.

In another paper at about the same time, Rolleston, H.D. (1910), delivered a total of four newborns who became jaundiced, and three of these died. The mother of these three newborns had herself become jaundiced late in the pregnancy. The fourth pregnancy resulted in a normal newborn infant who never became jaundiced. The cause of the jaundice was stated to be "obscure."

In spite of an increasing number of published reports of neonatal jaundice, the link between hyperbilirubinemia and brain damage was not made until 1914 (Guthrie, L. 1914). This paper describes a newborn infant with familial icterus gravis neonatorum (erythroblastosis fetalis). In this paper, the neurological features of hypotonia and chorioatetosis were described in the patient at the age of 19 months. The suggestion was made that these symptoms may represent a manifestation of brain damage by bilirubin, and Guthrie is thus credited as the first to publish a description of what is now known as kernicterus.

In 1932, a key paper was published (Diamond, L., Blackfan, K., and Baty, J. 1932) which defined and combined under one heading the clinical conditions of erythroblastosis fetalis, newborn anemia, edema of the fetus, and icterus gravis neonatorum. The exact cause of these disease entities, now under one heading was unclear since the concept of blood incompatibilities was not well understood. This, nevertheless furthered knowledge of anemia and resultant hyperbilirubinemia and kernicterus. When the pathology of hemolytic disease of the newborn was ultimately described, the techniques for exchange transfusion in newborn infants were developed. This facilitated the removal and replacement of damaged red blood cells. It also reduced levels of unconjugated bilirubin, proving to be a satisfactory treatment for the reduction of serum bilirubin levels, and a dramatic reduction of kernicterus.

As a side note, in 1944, Blackfan, K., Diamond, L., and Leister, C. published an atlas of blood disorders in children. Leister was an artist of considerable talent, and produced a series of beautiful water color paintings of blood smears which constitute most of the figures in the atlas and are used with permission in this volume (Blackfan, K., Diamond, L., and Leister, C. 1944, see chapter 5).

In 1950, Vaughan, V., Allen, F., and Diamond, L. published an important paper looking at the relation of erythroblastosis and kernicterus. They also reviewed various aspects of kernicterus as it was known at that time. Earlier studies had indicated that a Rh-positive fetus born to a sensitized Rh-negative mother was at risk, and that the chances of recovery were inversely related to the degree of anemia. Frequency of kernicterus, however, was not related to other signs and symptoms.

The incidence of reported kernicterus in early studies had a wide range, from 55% to as low as 10%. In the study by Vaughn, Allen, and Diamond, an incidence over 4 years was 12%, with 4.9% of kernicteric newborns surviving. All survivors

had some neurologic sequelae ranging from mild incoordination to severe motor disability and mental retardation.

The authors give a rather complete description of the clinical manifestations of kernicterus, which include developing jaundice on day 1, and by day 2–3 the jaundice becomes severe. This is accompanied by lethargy and poor feeding. Pathognomonic signs include a weakened or absent Moro response, and the presence of opisthotonic posturing. This includes rigidity and arm extension. It may also include brief high-pitched crying. Death in kernicterus is usually from respiratory failure, and seizures are not common, but do occur. Pulmonary hemorrhage is almost always associated with the end stages of kernicterus. Microscopically, the pathology consists of alveolar hemorrhage.

These authors found cerebral lesions in general agreement with those of early investigators. Specifically, lesions were found in the basal ganglia, hippocampus, cerebellum, olives, and medulla. These lesions were more diffuse in infants dying in 3 days or less, but were pronounced in newborns dying after 4–5 days. In infants surviving longer periods, the microscopic picture is one of neuron loss and glial proliferation. The location of the lesion is usually consistent with the signs and symptoms. Thus, newborn infants with motor involvement have lesions in the basal ganglia and cerebellum, whereas newborns with respiratory failure would show lesions in the medulla. (see Table 1 in the chapter “Neuropathology of Kernicterus”, this volume).

The paper also describes the increase in incidence of kernicterus in newborns born prematurely, before 38 weeks of gestation, whether naturally or prematurely due to induction in sensitized women. The increased risk for kernicterus offsets the potential gains achieved in the prevention of stillbirths.

Kernicterus seemed to be a disease of neonatal life, reinforced by the findings that at birth, infants destined for kernicterus showed normal neurological reactions for a time before jaundice became severe. This indicates the brain was not damaged prior to birth. This odd course predates the findings of Schenker, who showed that unconjugated bilirubin easily crosses the placenta (Schenker, S. 1963). It is thought that death in cases of erythroblastosis fetalis is rarely from anemia, but that the greater the anemia, the higher the risk for developing kernicterus, the major cause of death in these cases. The authors downplay other hypotheses such as kernicterus acts to plug cerebral vessels leading to hypoxia, or that antibody transfer into the fetus at labor could be involved in the development of kernicterus.

Another milestone occurred when it was learned that the bilirubin in serum actually existed in two phases. The usual method for measuring bilirubin was by a spectrophotometric method in which bilirubin was coupled with diazotized sulfanilic acid-diazo reagent. It was afterward realized that there were two types of reactions occurring. One was termed direct, the other indirect – the reaction only occurred after alcohol was added to the reaction. The reason behind this peculiar phenomenon was at the time unclear.

Subsequent chromatography work showed that there was a slow moving fraction which gave the indirect diazo reaction, and a fast moving fraction which was the direct moiety. In 1956, three laboratories independently solved the mystery by

showing that the direct moiety was formed by bilirubin glucuronide (Schmid, R. 1956; Talafant, E. 1956; Billing, B., Cole, P., and Lathe, G. 1956). Bilirubin glucuronide was a water-soluble form of bilirubin, and was easily excreted by the liver, as compared to the indirect form of bilirubin which was lipid soluble.

In another classic study, the protein binding of bilirubin was examined (Odell, G., 1959). Spectrophotometric studies showed that protein (albumin)-bound bilirubin was changed when organic anions such as salicylates and sulfonamides were injected into subjects. This was indicated by a drop in absorption at 460 m μ to values of from 420 μ to 440 m μ . The lower value is that which is associated with unbound unconjugated bilirubin.

The significance of this paper was to emphasize the competitive binding characteristics of certain organic ions such as sulfonamides and salicylates for albumin-binding sites. This acts to displace unconjugated bilirubin from albumin, facilitating its entry into brain structures, producing kernicterus. This also emphasizes the idea that simple measurement of total bilirubin levels may not be a completely accurate indication of kernicterus risk. A small dissociation constant for albumin-bound bilirubin would lead to a large percentage change in unbound bilirubin whenever there was a small increase in diffusible bilirubin.

Another very important paper was published in 1968 (Lucey, J., Ferreiro, M., and Hewitt, J. 1968). Dr Lucey's studies have centered on the prevention of hyperbilirubinemia and kernicterus in newborn infants using photo therapy. Prior to 1968, photo therapy had been used successfully in several countries in South America and Europe. There was some reluctance, however, for approval to be granted in the USA possibly due to uncertainty about potential undefined risks of photo therapy per se, and questions about the safety of the photo-degraded composition of products produced by the photo therapy.

Dr. Lucey and co-workers performed a controlled study in 111 newborn infants who were less than 2,500 g at birth. This was a randomized study in which newborn infants were assigned to either a photo therapy group, or to a control group. The assignments were made before 12 h of age. Results showed that the photo therapy treatment produced a statistically significant lowering of serum bilirubin between the fourth and sixth days. Furthermore, no correlation between the levels of albumin and the ability of photo therapy to lower serum bilirubin could be found.

No toxic effects were found which could be attributable to photo-degraded bilirubin products. Other authors had shown that photo-degraded products of photo therapy were rapidly excreted in bile and urine (Ostrow, J. 1967). This implies that the lipid-soluble nature of unconjugated bilirubin is rendered, by photo therapy, to water-soluble compounds which do not require conjugation in order to be excreted.

Since as many as 10% of preterm infants at this time had serum bilirubin levels over 20 mg/100 ml with significant risk for brain damage, the institution of photo therapy had the potential to reduce the risk of kernicterus to near zero. That is indeed what happened, and as stated in the chapter in this volume on photo therapy, the significance of this study, which demonstrated beyond doubt the safety of photo therapy, is immeasurable. Photo therapy has saved thousands of newborn infants from morbidity and mortality due to unconjugated bilirubin in the USA.

The study of Schenker, et. al. mentioned earlier, regarding the placental transfer of bilirubin was key in the understanding of why fetal hyperbilirubinemia was nonexistent, and answering in part why bilirubin levels tended to rise shortly after birth (Schenker, S., Dawber, N., and Schmid, R. 1964)

Advantage was taken of the availability of biosynthesized ^{14}C radiolabeled bilirubin. Radiolabeled unconjugated bilirubin, infused into fetal guinea pigs in vivo appeared in maternal bile as radiolabeled conjugated bilirubin. This excretion of fetal injected label began to appear in maternal bile within 15 min. Less than 2% of label appeared in fetal bile.

These results helped explain why fetal tissues are not stained in utero by unconjugated bilirubin. In regards to physiological and pathological hyperbilirubinemia, the results explain jaundice appearing within hours after birth. Since the placenta is a route for transfer of potentially toxic unconjugated bilirubin, the fetal liver is not significantly challenged as regards the enzymatic machinery (glucuronyl transferase) for conjugating bilirubin. At birth, the maternal mechanism for conjugating bilirubin is removed. This places a temporary but increasing load of bilirubin on the newborn liver. This had not been previously experienced by the liver, and a certain “lag” time exists in about 60% of newborn infants. Just a few days is enough to resolve the physiological unconjugated hyperbilirubinemia. In cases of hemolysis, the correction of hyperbilirubinemia may need clinical intervention.



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