9. Kernicterus (Bilirubin Encephalopathy)

The first report of kernicterus is widely attributed to Orth (1875), but his description is not clear and emphasizes superficial staining of the brain and the ventricular walls. The first comprehensive description of the disease was given by Schmorl (1903), who distinguished two types of cerebral lesions in icteric infants. One was a diffuse staining of the tissue in infants with periventricular infarcts. The other lesion, called kernicterus by Schmorl, was observed in six infants who had selective icteric discoloration of the subthalamic nuclei, Ammon's horn, lentiform nuclei, and dentate and olivary nuclei; the thalamus and cerebral cortex were spared. An intense yellow discoloration of many, though not all, of the nerve cells and a delicate staining of the intervening tissue were observed microscopically. Subsequent publications were reviewed by Zimmerman and Yannet (1933) and Pêhu and Dollet (1939). The term “kernicterus” is now used to designate the pathologic lesions as well as the clinical disease.

Kernicterus was considered a nosologic entity during the first part of the century. Many now obsolete hypotheses were proposed on its etiology. The discovery of the Rh factor by Landsteiner and Wiener (1940) opened the way for the recognition of kernicterus as a cerebral complication of icterus gravis. Fetal erythroblastosis is caused by isoimmunization of the mother by the Rh antigen of the fetus (Levine et al. 1941). Subsequent investigations made clear that kernicterus is a complication of infantile hyperbilirubinemia regardless of its etiology. The terms “bilirubin encephalopathy” (Waters et al. 1954) or “bilirubin toxicosis” (Chen 1964) were proposed. This lesion is extremely seldom in adults (Waser et al. 1986).

Metabolism of Bilirubin. The bilirubin formed from the breakdown of blood is normally taken up by the liver where it is conjugated with glucuronic acid. Conjugation is by means of a series of enzymatic reactions leading to the formation of uridine-diphosphate (UDP) glucuronide which serves as a donor of glucuronyl radicals for the formation of bilirubin diglucuronide. The reaction is mediated by UDP glucuronyl-transferase (Lathe and Walker 1958). The conjugated bilirubin is water-soluble and is excreted by the kidneys. Conjugated bilirubin is also called “direct reacting bilirubin”, in contrast to “indirect bilirubin” which is unconjugated and in plasma normally bound to serum albumin.

The significance of bilirubin production and the different steps of its elimination have been subject of extensive research. Most authors agree that the fundamental defect in neonatal hyperbilirubinemia is not hemolysis, but insufficient rates in the hepatic uptake of bilirubin, of bilirubin conjugation, and the excretion of bilirubin conjugates. The rate-limiting factor of bilirubin elimination appears to be the rate of synthesis of bilirubin conjugates due to low activities of hepatic glucuronyltransferase.
activity and ancillary enzymes (Lathe and Walker 1958). Glucuronide formation in the human newborn is 10% or less of the adult value; a postnatal increase of conjugation to normal adult rates has occurred by the third postnatal month (Vest 1958). The urinary excretion of conjugates is still lower in premature babies (Brown and Burnett 1957). No significant amounts of conjugated bilirubin are found in the plasma of children suffering from Rh or ABO incompatibility, or prematurity (Winsnes and Bratlid 1972). The lack in the enzymatic conjugation process is now widely accepted as the cause of neonatal hyperbilirubinemia. Any condition that induces hemolysis in the newborn adds to the load on the conjugation mechanisms already working at capacity, thus increasing the risk of kernicterus. Any factor inducing hepatic damage will further impair conjugation.

Hyperbilirubinemia may also result from an inherited defect of hepatic glucuronyltransferase as in familial nonhemolytic anemia, or as in rats of the Gunn strain. Deficient conjugation of bilirubin, therefore, emerges as a key factor in kernicterus, and it stands to reason that kernicterus does not develop in adults who have no conjugation defect, or in newborns suffering solely from congenital atresia of the bile ducts.

**Etiologies of Kernicterus.** Erythroblastosis fetalis or hemolytic anemias due to isoimmunization are caused in approximately 80% of cases by Rh incompatibility and in about 20% by the ABO system. Fetal erythroblastosis occurs in approximately 5% of parents, in whom the mother is Rh negative and the father Rh positive and in 1–5% of parents with the ABO constellation. Erythroblastosis due to Rh incompatibility is rare in the first pregnancy, because previous sensitization of the mother by a preceding pregnancy or by blood transfusion is required; jaundice develops during the 2nd to 5th day. ABO incompatibility occurs in the first pregnancy in 40–50% of cases; jaundice develops during the first 24 h and is associated with mild anemia and few other symptoms (Zuelzer and Cohen 1957).

The manifestation of kernicterus in erythroblastosis is related to the severity of the hemolytic anemia; it is likely to occur with serum bilirubin levels above 30 mg% and is rare at levels below 20 mg% (Hsia et al. 1952). The neurologic symptoms of kernicterus usually appear between the second and fifth day of life, with initial somnolence, apathy and hypotonia; disturbances of motor coordination, rigidity, opisthotonus, trismus, spasms, high-pitched cry or excitation lead to cyanosis and coma; convulsions are uncommon. A precipitous decrease in serum bilirubin may occur with the onset of neurologic symptoms (Ackerman et al. 1971). The prognosis is extremely poor after neurologic complications have developed, and the majority of infants die within the first or second week. Exchange transfusions prevent the development of kernicterus.

Another cause of kernicterus is severe hemolytic anemia in the newborn caused by erythrocyte deficiency of glucose-6-phosphate dehydrogenase in Mediterranean and Chinese populations in whom this defect is more prevalent. Jaundice and kernicterus may be precipitated by exposure to normally innocuous drugs, such as primaquine, sulfonamide, or naphthalene (Panizon 1960; Smith and Vella 1960; Naiman and Kosoy 1964). An increased incidence of kernicterus with high intake of vitamin K (Schall 1958) may also depend on increased hemolysis, but other pathogenetic factors may be involved as well.