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Theories regarding the pathogenesis of kernicterus

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THEORIES REGARDING THE PATHOGENESIS OF KERNICTERUS

The purpose of this thesis is to examine the available clinical and experimental data concerning the pathogenesis of kernicterus. Knowledge of the etiologic importance of incompatibility between the blood groups of the fetus and mother has been advanced greatly during the past fifteen years. However, the data of several groups bring out the association between jaundice and kernicterus in infants without hemolytic disease of the newborn and show that kernicterus may be more commonly a complication of so-called physiologic jaundice and prematurity than of isoimmunization.

Kernicterus has long interested clinicians, pathologists and hematologists. The first description of this unfortunate sequel to hemolytic disease of the newborn was by Orth (1) who used the term nuclear jaundice as long ago as 1875. He believed that there was a primary necrosis of parts of the brain and that these areas were subsequently pigmented. Schmorl (1), in 1903, introduced the term kernicterus in his description which was the first detailed report of the pathological features of the cerebral

lesions. He reported observations of bile staining in the basal ganglia, cerebellum and brain stem in a newborn infant with jaundice and suggested that the primary change was cell necrosis either resulting from vascular damage or from a toxic degeneration of the cell. He believed that the toxin responsible might be bile itself. Hart (1) also thought that the ganglion cells were injured by bile or became pigmented with bile following injury by some other unknown toxin.

The link between the liver and brain damage early attracted the attention of workers in this field. Hoffmann and Hausmann (2) in 1926 suggested that the liver damage took the form of a hepatitis which resulted in the liberation of lipolytic substances which, in turn, were responsible for cerebral necrosis from their toxic effect.

Several experimental workers investigated the possibility of liver disease leading to cerebral damage. Fuchs (1) in 1917 fed experimental animals guanidine and caused liver damage and subsequent changes in the brain. Pollak (1) in 1921 examined the brains of animals which had undergone such an experiment and found an inflammatory reaction in the

basal ganglia with neuronal loss. The damage was diffuse, however, and not wholly confined to the nuclear masses. Mella (3) injected manganese intra-peritoneally into Macacus rhesus monkeys and pro-duced nuclear loss in the putamen and caudate nuclei. In two of his animals hepatic fibrosis occurred. Crandall and Weil (4) ligated the common bile duct in rats and caused degeneration of the corpus stri-atum. While these experiments failed to reproduce kernicterus they did seem to indicate a link between hepatic dysfunction and cerebral damage.

As an alternative to the theory that kernicterus resulted from the action of a toxin on the basal ganglia, Schmorl (1) and Beneke (2) both suggested that vascular damage caused by thrombosis or other change led to ischemia of the nuclear masses and subsequently to pigmentation. Thorling (1) also thought that ischemia played a part and suggested a combin-ation of low blood pressure and respiratory failure as the underlying cause of ischemia. In the experi-mental field Spielmeyer (5) found that the corpus striatum and hippocampus have a relatively poor blood supply and are liable to damage in disease affecting their circulation. Meyer (6) showed that the globus

pallidus, inferior olives, dentate nuclei of the cerebellum and hippocampus are the most commonly injured parts when the brain was ischemic, whether this was caused by morphine, carbon dioxide or carbon monoxide poisoning. Wolff (1) also demonstrated that hypoxia affected these regions severely. These findings were interpreted as indicating that some type of vascular injury was essential before cerebral tissue could be induced to take up trypan blue which has been shown to resemble the action of bilirubin (1).

At one time neonatal sepsis was believed to be an etiological factor in the development of icterus gravis and of kernicterus. Beneke (2) believed that organisms entered the blood stream via erosions in the gastric mucous membrane. Knoepfelmacher (1), Pfaltzer (1) and Thorling (1), all obtained positive cultures from post mortem material in kernicterus cases and were strongly in favor of an infective basis for the disease. Dunham (7) found jaundice in fourteen instances in forty cases of neonatal sepsis. Zimmerman and Yannet (8) obtained E. Coli from the blood in two cases of kernicterus and were inclined to favor the sepsis hypothesis of the development of kernicterus. Biemond and van Creveld (9) reported

two cases of kernicterus and icterus gravis where severe umbilical sepsis was present. In a series of four cases of kernicterus by de Bruyne and van Creveld in 1948 (10) severe umbilical sepsis was present in all cases. However, evidence of isoimmunization was found to be present in two mothers, thus casting some doubt on the validity of the infective hypothesis.

Orth (1) in 1875 also had suggested that there might be some "congenital inferiority" of the brain predisposing to the localization of bile in the nuclear masses. This suggestion has received support. Fitzgerald et al. (11) believed that the degree of "maldevelopment" was a primary factor in the onset of kernicterus. Frolich and Mirsky (12) produced convulsions in young rats but not in older ones by administration of bilirubin. Vaughan (13) was inclined to believe that "immaturity of cerebral and cerebrovascular tissue" played a part in the etiology of kernicterus. Lande (14) thought that in some families the nervous system was more liable to toxic or emotional upset than in others which could predispose to kernicterus.

With the discovery of the Rh blood groups a great impetus was given to the study of the disease process

and many workers attempted to establish a relationship between vascular changes and the development of kernicterus. Diamond and Denton (15) suggested that the terminal capillaries to the nuclear masses might become blocked by cel ular debris resulting from hemolysis. Wiener (16) in his theory concerning the pathogenesis of hemolytic disease of the newborn postulated that these terminal capillaries became blocked by agglu ination thrombi with subsequent cerebral damage. However, there is no histologic evidence to support this theory (13) and Wiener later retracted the thrombosis theory (17).

The discovery of the Rh blood groups explained the familial incidence of the disease which had baffled so many previous investigators. In was then shown that the antibody in the mother's serum acted on the antigen of the infant's red cells causing their hemolysis. This has led some authors to suggest that a direct antigen-antibody reaction occurs in kernicterus with the cerebral cells acting as the antigen. Yannet and Lieberman (18) believe that this possibility exists, but there is no clear proof that such antigen is present in the cerebral neurons or that such a reaction occurs.

Darrow (19) has suggested that anaphylaxis might play a part in the etiology of kernicterus. Recently, Darrow and Chapin (20) have repeated the suggestion that in addition to the antigen-antibody reaction there is an anaphylactic process which accounts for the onset of icterus gravis and the development of kernicterus in some cases. Their explanation of the development of hemolytic disease of the newborn is not very convincing.

One of the problems that needed clarification was whether the pigmentation of the nuclear masses is a primary occurrence or is secondary to nerve cell injury. Zimmerman and Yannet (8) state the opinion that following some injury the nerve cells are subsequently stained with blood borne bile pigments. Vaughan (13) believes this view to be most reasonable. The ganglion cells are damaged first and thereafter assimilate bilirubin to a greater extent than the surrounding areas which are undamaged.

Yannet and Lieberman (18) believe that cerebral injury is entirely secondary to the destruction of red blood cells during certain periods of fetal life. The resultant anoxemia causes permanent injury to the developing neuron and the cerebral damage is well

established before birth. This belief is also supported by Parsons (21) who views the sequence of events in kernicterus as an antigen-antibody reaction between the liver cells and the Rh antibody resulting in necrosis of the liver cells followed by necrosis of brain cells which then become stained by the bile pigment--Parson's hepatic encephalopathy theory. Kernicterus is not due to hemolysis as there is no parallelism between the degree of hemolysis, the severity of the jaundice and the presence of kernicterus. Cappell (22) has stated that if the neurons are damaged during fetal life it is remarkable that no histologic evidence of neuroglial reaction to neuronal death is present in the brains of infants who die within the first day or two of life.

Claireaux (1) recalls the experimental work of Speilmeyer (5) and Meyer (6) who showed that the areas involved in kernicterus are those most commonly injured by anoxia of cerebral tissue and concurs with theory that the antigen-antibody reaction in the fetus results in the production of a sufficient degree of anemia to cause cerebral anoxia. Mollison and Cutbush (23) show that some degree of anemia is present in nearly all cases of icterus gravis resulting from

hemolytic disease, but this anemia may be concealed in the early stages. Claireaux concluded, therefore, that the anoxia is responsible for the original cell damage which leads to subsequent pigmentation. This damage is of such a nature that the cell is not destroyed but is sufficiently changed to permit the bile staining to occur. The oxygen lack is sufficiently severe to render the cell membrane permeable to bilirubin but is not so great as to cause cell death. Once pigmentation has occurred, the combination of anoxia and the presence of pigment in the cell eventually leads to the death of the cell towards the end of the first week of life. Thereafter the affected nuclear masses undergo gradual astrocytic replacement and the typical neurological signs of the condition become apparent. He regarded kernicterus to a complication only of icterus gravis resulting from hemolytic disease of the newborn.

The presumed sequence of severe anoxia or other brain injury followed by staining of damaged neurons received support from at least two experiments. Day (24) produced kernicterus by injuring one of the cerebral lobes of rats with roentgen radiation. Jaundice was then produced by the occlusion of the common bile

duct and intravenous injections of bilirubin. Vogel (25) injected bilirubin into the umbilical veins of rat fetuses and kernicterus developed in the younger animals following partial occlusion of the umbilical circulation for periods of thirty to forty minutes. Kernicterus could not be produced without impairment if circulation. Such experiments indicated that if brain tissue is sufficiently damaged it will be stained by circulating bilirubin.

It has been pointed out (26) that the very infants who supposedly show the greatest evidence of such damage--the premature infants without hemolytic disease--belong to the group of infants probably most resistant to such injury. In animal experiments it has been demonstrated (27) that newborn mice, rats, rabbits and dogs are capable of surviving anoxia for periods forty times greater than those fatal to adults of the same species. The ability to survive anoxia is quickly lost so that, for example, by the tenth to the sixteenth post-natal day newborn rats have achieved parity with adults. In man the maximum anerobic survival time of the newborn consistent with little or no detectable cerebral damage is unknown. It is well known, however, that the newly born infant shows a

remarkable resistance to anoxia. This is believed to be due to the persistance, as in the rat, from the fetal into the neonatal period, of a relatively more anerobic carbohydrate metabolism than exists in the post-newborn period (27).

Among the animal groups the greater the prematurity, the greater is the resistance to anoxia. If this relation should be true of man, it seems improbable that anoxia in the absence of other injury would damage the brain of the premature infant more readily and frequently than that of the mature infant (26).

Kuster and Krings (28) have suggested that bilirubin itself, in excess, may cause cerebral damage. They were able to produce kernicterus in the experimental animal by the intravenous injection of bilirubin. However, the high levels needed--100 to 150 mg. per 100 ml.--are much greater than those encountered in icterus gravis with or without kernicterus (2).

Gerrard (2), because of reports in the literature of hypoglycemia plus large and numerous islets of Langerhans associated with hydrops fetalis and kernicterus, decided to follow blood sugar levels in cases of hemolytic disease in order to determine if

hypoglycemia had a role in the production of kernicterus. A considerable fall in the blood sugar level was noted in a number of cases of hemolytic disease and in six of the forty cases studied the blood sugar fell below 30 mg. per 100 ml. One might suppose that hypoglycemia may lay a part in the production of kernicterus and that, in conjunction with anoxia and the toxic action of bilirubin, it may lead to the destruction of those nuclear masses which, especially in the newborn period, are developing most rapidly and have great metabolic requirements. However, this theory is difficult to sustain, for the infant who was most anemic at birth also experienced a marked hypoglycemia and yet did not develop kernicterus, while another infant, who was never very anemic, experienced no hypoglycemia and developed kernicterus.

Claireaux (1) as late as 1950 made the dogmatic statement that kernicterus is always seen with icterus gravis arising from hemolytic disease of the newborn. This view was commonly held then even though Vaughan (13) in 1946 said that he had observed kernicterus in two premature infants under circumstances where there was no possibility of Rh sensitization. Parsons (21) cited two similar cases in 1947. Late in 1950

and maternal diabetes. Prematurity was present in about seventy-five percent of the cases. These investigators considered that since prematurity in itself is apparently not a cause of kernicterus it must be regarded as a predisposing factor. The variety of pathologic states found by the authors in association with kernicterus, while doubtful if they can be regarded as direct etiologic factors, suggested the possibility that kernicterus does not represent a specific entity, but a non-specific mechanism. They regarded the coincidence of brain damage and bilirubinemia as the common denominator responsible for nuclear staining in an otherwise heterogenous group of newborn infants.

In 1953 Govan and Scott (31) reported ten cases of their own of premature infants with kernicterus without blood group incompatibility. They point out two important clinical differences between kernicterus due to erythroblastosis and kernicterus of prematurity. Infants with kernicterus due to erythroblastosis are usually mature and jaundice is an early feature whereas in their series it was delayed until the fourth day. Despite these clinical differences, however, the microscopic changes were almost identical

in both groups. There seemed to be less vascular disturbance in the erythroblastotic type, but the features reported by other workers were the same as those found in their series of premature infants. This prompted Govan and Scott to investigate any possible connection between the two groups. They studied the brains from non-jaundiced premature infants and found that brain lesions occur in this group in the absence of liver dysfunction and the pigment is deposited secondarily in areas already damaged which coincides with Cappell's observations (22) in the erythroblastotic infant. Thus having ruled out hepatic damage as a cause of the brain lesions they found that the only significant feature common to both groups of infants was difficulty in resuscitation at the time of birth. This would inevitable lead to anoxia. The pathologic changes described in conditions of central nervous system anoxia from morphine, carbon monoxide and potassium cyanide poisoning, diabetic coma and asphyxia due to nitrous oxide anesthesia were found to be very similar to those found in kernicterus and the distribution of the lesions were identical.

Thus, from a consideration of the changes described and the findings in comparable conditions,

they concluded that the main factor in the production of the lesions found in kernicterus in premature infants is anoxia and in view of the similarity of histologic changes and anatomic distribution of lesions, and the absence of any correlation between the occurrence of brain lesions and the titer of antibody or degree of erythroblastosis, it seemed probable to them that anoxia is the important factor in the latter group also.

Black-Schaffer et al. in 1954 (26) reported thirteen cases of kernicterus without hemolytic disease among the dead newborn infants of a Japanese community and they came to the conclusion that physiologic jaundice is responsible for more cases of kernicterus than is hemolytic disease of the newborn. They suggest that indirectly severe hypoxemia may contribute to the production of kernicterus through the impairment of liver function and the elevation of the serum bilirubin level. This mechanism may be extremely significant in prematurity where periods of apnea and cyanosis are not uncommon.

Sutow et al. (32) recently reported clinical and serological data from twenty-five cases of kernicterus found among Japanese infants necropsied by

the Atomic Bomb Casualty Commission in Hiroshima Nagasaki, Japan. All except one occurred in the absence of serological evidence of hemolytic disease of the newborn due to isoimmunization.

Because kernicterus is associated with both physiologic jaundice and the icterus of erythroblastosis fetalis, it would be well to examine the genesis of these two forms of neonatal jaundice.

The genesis of physiologic jaundice was reviewed by Weech (33) who concluded that physiologic jaundice was largely due to retention by the immature liver of physiologically produced bilirubin and consequently, "the behavior of the infant with respect to bilirubin is largely predetermined at the time of birth." He found that the highest serum bilirubin among ninety-four term infants was 26.2 mg. per 100 ml. Concerning the origin of the bilirubin it has been demonstrated (26) that in adults at least eleven percent of the circulating bilirubin is derived from sources other than mature erythrocytes and marrow cells, catalase, myoglobin, peroxidase and the cytochromes may be other sources. The role of these in neonatal jaundice is not known.

In 1930 Rich (34) described neonatal icterus as

a retention jaundice due to the inability of immature liver to excrete the bilirubin liberated by the destruction of the excess erythrocytes of fetal life and emphasized the fact that icterus neonatorum is especially common in premature infants. He stated that a normal liver is capable of excreting, without jaundice, far more bilirubin than it commonly receives.

In contrast to the above views the pathogenesis of the jaundice of hemolytic disease of the newborn is commonly attributed to excessive hemolysis re-sulting from the action of the maternal Rh antibody upon the infant's Rh positive red cells (1, 31). This mechanism, Black-Schaffer states (26), is important, but that it is the only, or even a significant cause of hyperbilirubinemia in any given Rh positive infant of a sensitized Rh negative mother is questionable. If the pathogenesis were this simple, the Rh anti-body adsorbed upon the infant's red cells (Coomb's test) should always be demonstrable. Furthermore the intensity of this test should be very closely related with both the degree of hemolytic anemia and the degree of bilirubinemia. Actually, these correlations are sometimes completely absent or of such low order as to prohibit definite conclusions (26).

Vaughan and co-workers (13) wrote that the Coomb's test had not proved an accurate index of the severity of hemolytic disease and that in at least two cases of kernicterus with hemolytic disease it had been completely negative. The same group in another paper wrote that the incidence of kernicterus was virtually independent of the degree of anemia and that there was no evidence in his series that the Coomb's test had any relation to the severity of the disease. The authors report seeing babies with strongly positive Coomb's tests who had no clinical disease, as well as a few in whom a negative Coomb's test was associated with a fatal case of kernicterus. In hemolytic anemia of the newborn the converse has been observed repeatedly, namely, a progressive but self-limiting anemia in Rh positive infants of sensitized Rh negative mothers with the development of little or no jaundice (35).

Brown and Zuelzer (36) feel that a redefinition of physiologic jaundice is needed. In their opinion the hyperbilirubinemia associated with neurologic sequelae is different from that commonly seen in the newborn and just because the mechanism of the pathologic hyperbilirubinemia cannot now be disting-

uished from that responsible for the lower degrees of bilirubinemia, one should not speak of physiologic icterus in a group whose bilirubin values deviate so markedly from the average. They feel that knowledge of the role of the liver and of the possible enzyme systems involved in the metabolism of bilirubin, the influence of prenatal and paranatal factors, including placental function, on the development of the abili y to metabolize bilirubin seems indicated for an understanding of the mechanism of hyperbilirubinemia.

On the basis of the work of Weech and Rich, Black-Schaffer (26) attempts to explain, at least in part, the apparent paradoxes in hemolytic disease of the newborn. Approximately fifty percent of all infants develop physiologic jaundice (27). The hyperbilirubinemia reaches its peak between the second and fourth postnatal days depending directly on its initial height. This has been confirmed by Hsia (37). This is true of infants regardless of the presence or absence of isoimmunization. Thus, in about one half of all cases of hemolytic disease there exists, in addition, the probability of physiologic jaundice. Knowing that physiologic jaundice may occasionally

be severe, it becomes evident that an Rh positive fant or a sensitized Rh negative mother may develop intense jaundice and even kernicterus without actually having hemolytic disease. In contrast, the occurrence of hemolytic disease without significant jaundice may be interpreted as indicating that, in the presence of adequate liver function, jaundice need not develop.

It can be assumed that in hemolytic disease of newborn, the more Rh antibodies adsorbed to the infant's red cells, the more severe the hemolysis and the greater the production of bilirubin. At this point the degree of maturity of the liver will determine to a large extent the presence or absence of neonatal jaundice in the premature infant, the term infant or the infant with hemolytic disease. Thus, in hemolytic disease all degrees of correlation may exist between the Coomb's test, anemia and bilirubinemia without necessarily posing a paradox. Since in the first postnatal days the newborn liver tends to excrete bilirubin poorly, the more bilirubin produced, the greater the probability of developing marked jaundice. This is usual in the case of hemolytic disease. The less mature the liver, as in prematurity, the more intense is the jaundice even without undue

hemolysis and the more severe its complications. It is evident that the most unfavorable course will occur in the premature infant with hemolytic disease and this has proved to be the case (26).

Each hypothesis in explanation of the pathogenesis of kernicterus has its merits. However, it would seem that several well documented observations must be adequately explained before any one may be considered correct. These are:

1. Kernicterus does not develop before birth.

2. Kernicterus does not develop after the first few days of neonatal life.

3. Premature and some term children without hemolytic disease of the newborn may develop kernicterus.

4. Exchange transfusions have effectively reduced the incidence of kernicterus in hemolytic disease of the newborn.

If kernicterus is the result of a mass action effect of the bilirubin, obviously it cannot occur when the bilirubin blood level is low. All studies of cord blood bilirubin levels show that it rarely rises above 10 mg. per 100 ml. (38, 33, 37). There is evidence, though inconclusive, that this limita-

tion is due to placental excretion of bilirubin (39). Since kernicterus is most apt to occur when the bilirubin rises above 30 mg. per 100 ml. and is unlikely to occur if it remains below 20 mg. per 100 ml., it is apparent that kernicterus will not occur in utero (38, 37)

In man, kernicterus, as it appears in the newborn, has never been described as developing in the post-newborn period. It would appear that the common finding of kernicterus in the premature infant and the infants with hemolytic disease must depend upon some factor or factors characteristic of the neonatal period.

Concerning the third observation, that premature and some term infants develop kernicterus without much hemolysis, it bears repeating that in the infant with hemolytic disease there exists a high correlation between the intensity of the bilirubinemia and kernicterus (13). In addition it has been demonstrated that the birth serum bilirubin levels of premature infants without hemolytic disease parallel those in hemolytic disease (13).

That hyperbilirubinemia is alone associated with kernicterus is demonstrated by the case of Crigler

and Najjar (40). They discovered within a family group an inherited bilirubin excretion defect of the liver. Among the members of this family, one case of kernicterus was demonstrated and a number of those affected developed the neurologic signs characteristic of kernicterus. All members of the family were Rh positive and isoimmunization could not be demonstrated. Full term mature children without hemolytic disease with kernicterus may be analogous to the case cited by Weech (33) of a full term infant who developed severe physiologic jaundice with a serum bilirubin level of 40 mg. per 100 ml. who developed the neurologic signs of kernicterus and was permanently crippled. The child was Rh and ABO compatible and was never anemic.

The reduction in the number of kernicteric babies after exchange transfusions in hemolytic disease of the newborn can only be explained by a mechanism which prevents severe brain injury preceding the staining of the nuclear masses (41). If the brain were severely injured prior to staining, this injury should persist despite exchange transfusion and the incidence of dead and neurologically damaged babies would remain unaffected. The effective reduction of the mor-

bidity and fatality rate of kernicterus is a strong point against the "preceding anoxia" school of thought (26).

Two investigators have presented very interesting theories relating the placenta to the pathogenesis of kernicterus. Bevis (39) believes that kernicterus is an antenatal disease despite the fact that no case of kernicterus has been demonstrated in a stillborn infant. The probable explanation of this is that the placenta is able to deal with these pigments while the child is in utero, but after delivery the accumulation of pigments results in the appearance of clinical signs of kernicterus. He states that the production of pigments is inhibited by the enzyme catalase and has been able to demonstrate tha the catalase content of the placenta is appreciably reduced in the sensitized Rh negative woman. He therefore postulates that the Rh antigen-antibody reaction in the sensitized Rh negative woman results in a diminution of the catalase content of the placenta possibly by poisoning of the enzyme by increased amounts of iron. This reduction in available catalase results in increased production of pigment and the classical signs of kernicterus are produced.

Saunders (42) postulates that since kernicterus makes its appearance a few days after birth it might be due to the withdrawal of an inhibiting or neutralizing substance or substances present in utero but unavailable to the infant after birth. This substance might originate in the placenta and by its presence prevent kernicterus in the unborn infant. The withdrawal of this factor after birth may then allow kernicterus to develop within a few days.

On this hypothesis placental extract was administered to a group of infants with hemolytic disease by intramuscular injection of one ml. morning and evening from birth to five to six days of age. Though his results were inconclusive they would appear to warrant further investigation.

The nature of the pigment in kernicterus is not yet firmly established, but the assumption has been that it is bilirubin or a derivative. Claireaux et al. (43) studied the brain pigment from four newborn infants representing kernicterus from isoimmunization and kernicterus from physiologic jaundice. From a study of the diazo reaction, the chromatographic behavior and the absorption spectrum they concluded that the pigment in each type of case is bilirubin.

Bevis (39), analyzing the yellow pigment in the brains of two cases of kernicterus (methods of analysis not given) showed that the pigment of icteric brain is mesobilifuscin. No experimental evidence to this effect has been presented. Claireaux states (43) that mesobilifuscin, the nature of which is very obscure, does not give a diazo reaction and unlike Bevis found that the brain pigment reacts positively, as does bilirubin.

In contrast to the brain extracts from Claireaux's cases in which bilirubin (the indirect reacting fraction) greatly predominated, extracts of serum from other cases of hemolytic disease had a larger proportion of the direct reacting bile pigment and he postulates that the brain seems to have a selective attraction for bilirubin due to his finding that brain tissue contains a bilirubin-retaining lipid. This lipid seems to have no affinity for direct reacting bile pigment. It appears that it is the indirect and not the direct reacting fraction of pigment which produces brain damage which would explain why kernicterus does not appear in the more pronounced jaundice of adult patients with obstruction or in congenital atresia of the bile ducts in the newborn

where the pigment is predominantly direct reacting (43). Claireaux believes that conversion of bilirubin to the direct reacting pigment tends to protect the neonatal brain from kernicterus and that it is the function of the liver to change free bilirubin to the direct reacting pigment. Hence, a defect of this conversion may be the primary factor leading to kernicterus in premature infants in whom no increased production of bilirubin has been demonstrated.

Recently, Billing and Lathe (44) have indicated that the excretion of indirect bilirubin involves its conversion to a direct reacting water soluble pigment and that the main pathway is probably through conjugation with glucuronic acid. This conjugation is further confirmed by the recent work of Schmid (45) who has found that hydrolysis of the azopigment of direct bilirubin yields the azopigment of indirect bilirubin and glucuronic acid.

Experimentally, Day (46) has shown in vitro that bilirubin is inhibitory, though not lethal, for fresh tissue and for protozoa. The protozoa is maintained if equimolar concentrations of cytochrome C are added to the bilirubin. Similarly he reported that cytochrome C will restore oxygen uptake rates to normal after

rat brain has been inhibited by bilirubin. The reversal by cytochrome C suggested competition between that substance and bilirubin.

Recently, however, Bowen and Waters (47) have suggested from experiments that instead of inhibition taking place at the cytochrome level, it takes place at the pyridine nucleotides (DPN AND TPN) level and is reversible.

CONCLUSION: Although many theories and speculations regarding the pathogenesis of kernicterus have been proposed it would appear that much more clinical and experimental investigation remains to be done before a generally acceptable explanation can be furnished. Kernicterus seemingly occurs in the newborn group with the greatest hyperbilirubinemia. Among full term infants, it is most often a complication of the jaundice associated with hemolytic disease of the newborn. Among premature infants it is usually a complication of physiologic hyperbilirubinemia and according to many, this group is the larger. In addition, the presence of any lesion tending to reduce the level of liver function, for example, infection, might well contribute to a further rise of serum bilirubin, increasing the possibility of kernicterus without

known or demonstrable direct effect upon the brain. It would appear that the role of the liver holds the key in the ultimate solution of this problem.

Finally, physicians and students should be made aware that kernicterus may occur, not only as a complication of hemolytic disease of the newborn, but also of other conditions as well.

BIBLIOGRAPHY

1. Claireaux, A., Hemolytic Disease of the Newborn; Part II: Nuclear Jaundice, Arch. Dis. Childh. 25: 71, 1950.

2. Gerrard, J., Kernicterus, Brain 75:526, 1952.

3. Mella, H., The Experimental Production of Basal Ganglion Symptomatology in Macacus Rhesus, Arch. Neurol. Psychiat., Chicago, 11:405, 1924.

4. Crandall, L.A., and Weil, A., Pathology of Central Nervous System Disease of the Liver, Arch. Neruol. Psychiat., Chicago, 29:1066, 1933.

5. Spielmeyer, W., The Anatomic Substratum of the Convulsive State, Arch. Neurol. Psychiat. Chicago, 23:869, 1930.

6. Meyer, A., The Selective Regional Vulnerability of the Brain and its Relation to Psychiatric Problems, Proc. Roy. Soc. Med., 29:1175, 1936.

7. Dunham, E.C., Septicemia in the Newborn, Am. J. Dis. Child,, 45:229, 1933.

8. Zimmerman H.M., and Yannet, H., Kernikterus, Am. j. Dis. Child., 45:740, 1933.

9. Biemond, A., and van Creveld, S., Nuclear Jaundice in Neonatal (Umbilical) Sepsis with Jaundice, Arch. Dis. Childh., 12:173, 1937.

10. Bruyne, J.I. de, and van Creveld, S., On the Cause of Nuclear Jaundice in Neonatal Sepsis with Jaundice, Arch. Dis. Childh., 23:84, 1948.

11. Fitzgerald, G. M., Greenfield, J.G., and Kouine, B., Neurological Sequelae of "Kernicterus" Brain 62:292, 1939.

12. Frohlich, A., and Mirsky, I.A., Susceptibility to Convulsions in Relation to Age: II. Influence of Bi e in Rats, Proc. Soc. Exp. Biol. and Med., N.Y., 50:25, 1942.

13. Vaughan, V.C., Kernicterus in Erythroblastosis Fetalis, J. Pediat., 29:462, 1946.

14. Lande, L., Clinical Signs and Development of Survivors of Kernicterus due to Rh Sensitization, J. Pediat., 32:693, 1948.

15. Diamond, L.K., and Denton, R.L., Rh Agglutination in Various Media with Particular Reference to the Value of Albumin, J. Lab. Clin. Med., 30:821, 1945.

16. Wiener, A.S., Pathogenesis of Congenital Hemolytic Disease (Erythroblastosis Fetalis). I.Theoretical Considerations, Am. J. Dis. Child., 71:14, 1946.

17. Wiener, A.S., and Gordon, E.B., Studies on the Conglutination Test in Erythroblastosis Fetalis, J. Lab. Clin. Med., 33:181, 1948.

18. Yannet, H., and Lieberman, R., Central.Nervous System Complications Associated with Kernicterus, J.A.M.A., 130:335, 1946.

19. Darrow, R.R., Icterus Gravis (Erythroblastosis) Neonatorum, Arch. Path., 25:378, 1938.

20. Darrow, R.R., and Chapin, J., Pathogenesis of Passive Rh Isosensitization in the Newborn (Erythroblastosis Fetalis) Am. J. Dis. Child., 73:257, 1947.

21. Parsons, L.G., The Clinician and the Rh Factor, Lancet 1:815, 1947.

22. Cappell, D.F., Kernicterus or Nuclear Jaundice, Lancet 2:444, 1947.

23. Mollison, P.L., and Cutbush, M., Hemolytic Disease of the Newborn: Criteria of Severity, Brit. Med. J., 1:123, 1949.

24. Day, R., Kernicterus Problem: Experimental in Vivo and in Vitro Staining of Brain Tissue with Bilirubin, . J. Dis. Child., 73:241, 1947.

25. Vogel, F.S., Studies on the Nature and Deposition of Kernicterus Pigment, Am. J. Path., 29:582, 1953.

26. Black-Schaffer, B., Kambe, S., Furuta, M., Moloney, W.C., Neonatal Jaundice and Kernicterus, Am. J. Dis. Child., 87:737, 1954.

27. Smith, C.A., The Physiology of the Newborn Infant, Ed. 2, Springfield, Ill., Charles C. Thomas, Publisher, 1951 p. 141.

28. Kuster, F., and Krings, H., Blood Destruction and Cerebral Damage in Hemolytic Disease of the Newborn, Lancet 1: 979, 1950.

29. Aidin, R., Corner, B., and Tovey, G., Kernicterus and Prematurity, Lancet 1:1153, 1950.

30. Zuelzer, W.W., and Mudgett, R.T., Kernicterus; Etiologic Study Based on Analysis of 55 Cases, Pediatrics 6:452, 1950.

31. Govan, A.D.T., and Scott, J.M., Kernicterus and Prematurity, Lancet 1:611, 1953.

32. Sutow, W.W., Moloney, W.C., Margoles, C., Kernicterus in Japanese Infants. I. Clinical and Serological Data from 25 Patients, Pediatrics 17:349, 1956.

33. Weech, A.A., The Genesis of Physiologic Hyperbilirubinemia, in Advances in Pediatrics, edited by S.G. Levine, A.M. Butler, L.E. Holt, Jr., and A.A. Weech, New York, Interscience Publishers, Inc. 1947, vol. 2.

34. Rich, A.R., The Pathogenesis of the Forms of Jaundice, Bull. Johns Hopkins Hosp., 47:338, 1930,

35. Diamond, L.K., Vaughan, V.C.III, Allen, F.H., Erythroblastosis Fetalis. III: Prognosis in Relation to Clinical and Serologic Manifestations at Birth, Pediatrics 6:630, 1950.

36. Brown, A.K., and Zuelzer, W.W., Studies in Hyperbilirubinemia: I. Hyperbilirubinemia of the Newborn Unrelated to Isoimmunization, Am. J. Dis. Child., 93:263, 1957.

37. Hsia, D.Y-Y., Allen, F.H. Jr., Gellis, S.S., and Diamond, L.K., Erythroblastosis Fetalis. VIII: Studies of Serum Bilirubin in Relation to Kernicterus, New Eng. J. Med., 247:668, 1952.

38. Hsia, D.Y-Y., Allen, F.H. Jr., Diamond, L.K., and Gellis, S.S., Serum Bilirubin Levels in the Newborn Infant, J. Pediat., 42:277, 1953.

39. Bevis, D.C.A., The Mechanism of Production of Kernicterus, J. Obst. & Gynaec., Brit. Emp., 59:857, 1952.

40. Crigler, J.F. Jr., and Najjar, V.A., Congenital Familial Nonhemolytic Jaundice with Kernicterus, Pediatrics 10:169, 1952.

41. Mollison, P.L., and Walker, W., Controlled Trials of the Treatment of Hemolytic Disease of the Newobrn, Lancet 1:429, 1952.

42. Saunders, C., Kernicterus, Lancet 1:799, 1953.

43. Claireaux, A.E., Cole, P.G., and Lathe, G.H., Icterus of the Brain in the Newborn, Lancet, 2:1226, 1953.

44. Billing, B.H., and Lathe, G.H., The Excretion of Bilirubin as an Ester Glucuronide Giving the Direct van den Bergh Reaction, Proc. Biochem. Soc., Biochem. J., 63:6p, 1956.

45. Schmid, R., Direct Reacting Bilirubin, Bilirubin Glucuronide in Serum, Bile and Urine, Science 124:76, 1956.

46. Day, R., Kernicterus: Further Observations on the Toxicity of Heme Pigments, Pediatrics 17:925, 1956.

47. Bowen, W.R., and Waters, W.J., Bilirubin Encephalopathy: Studies Related to the Site of Inhibitory Action of Bilirubin on Brain Metabolism, Am. J. Dis. Child., 93:21, 1957.