BILIARY OBSTRUCTION ASSOCIATED WITH ICTERUS GRAVIS NEONATORUM

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For twenty years it has been known that obstructive jaundice may occasionally be seen in icterus gravis neonatorum. Still (1927) quoted the view that the bile of excessive haemolysis becomes too viscid to pass freely along the ducts, and he mentions the low pressure at which it is secreted. This view does not altogether explain the facts, because a marked obstructive phase does not necessarily go with the greatest haemolysis or the deepest preceding jaundice. MacClure (1931) suggested that the presence of a foreign substance in the bile caused coagulation in the bile capillaries. We favour a third possibility—namely, that biliary obstruction is due to swelling of damaged hepatic cells—because histological studies of icterus gravis show that such an association exists. The association is seen also in conditions other than icterus gravis, for example, stagnation of bile may be seen just outside areas of maximal necrosis in infective hepatitis.

Skelton and Tovey (1945) postulate two forms of biliary obstruction in association with icterus gravis: (a) blockage of one of the larger bile ducts with inspissated bile; and (b) conversion of the bile ducts into a fibrous cord. First let us consider the latter, that is, atresia of the bile ducts associated with icterus gravis.

Biliary Atresia Associated with Icterus Gravis Neonatorum

Pasachoff (1935) reported the case, fatal at the age of five days, of a coloured girl who some twelve hours after birth had deep jaundice, hepatosplenomegaly, and erythroblastosis, yet no anaemia. On the fourth day haemorrhage appeared and the stools were white. A moderate degree of anaemia developed. Necropsy showed extensive extramedullary haematopoiesis, kernikterus, complete atresia of the bile ducts, and cerebral aplasia. This case was reported in the pre-Rh period, and, therefore, the diagnosis of icterus gravis, though probably correct, could not be established beyond all doubt.

H. N. Sanford (1940) reported the case of an infant who at the age of two hours had marked anaemia (red blood cells 1,600,000 per c.mm.) and erythroblastosis (nucleated red blood cells 162,000 per c.mm.). The icteric index was 500 units (35 mg. per 100 c.cm.). Professor Sanford kindly sent the pathologist's report to one of us (R. L.) and we quote: 'The whole of the gall-bladder is slightly thickened and the lumen contains approximately 1 c.cm. of thick stringy bile; practically complete stenosis is seen, and this is traced to the ampulla of Vater. A probe can be inserted into the ampulla for a distance of three millimetres. The cystic duct is so small that a small probe cannot be passed. The same is true of the patent common duct. The lumen of the common bile duct is a few millimetres in diameter.' The mother was Rh-negative, the father Rh-positive, and another child born two years later also Rh-positive; this one developed a typical erythroblastosis foetalis at birth. Sanford concludes that the first baby was a case of 'atresia' of the bile ducts associated with erythroblastosis foetalis yet we cannot entirely concur with this view. It appears from the pathologist's report that this was not a case of atresia of the bile ducts but one with some degree of stenosis, which is not very infrequent. Again, the diagnosis of erythroblastosis foetalis, since it occurred in the pre-Rh period, was not quite proven. The latter child of this family was tested for the Rh factor and the mother found to be Rh-negative, but there is no report that she developed anti-Rh agglutinins.

Skelton and Tovey (1945) report two cases of erythroblastosis foetalis associated with congenital atresia of the bile ducts:

FAMILY G. E. The patient, a second child (the first was normal), developed jaundice on the first day, passed bile in the urine, and died aged two days; no blood count was reported. Necropsy disclosed erythroblastosis, marked erythropoiesis in the liver and spleen, fibrous obliteration of the common bile duct, and kernikterus. The father was Rh-positive; the child's Rh factor was not examined (this was in 1942). The first-born child was subsequently examined and found to be Rh-positive, the mother was Rh-negative, and no antibody was demonstrable three years after the birth of the affected child.

COMMENT. We think that in this case no final proof of the association of the two conditions has
been given. The child was not tested for the Rh factor, anaemia is not mentioned as a clinical feature, no Rh antibodies were found in the mother's serum three years after the birth of the child, and the mother's serum was apparently not tested at the time when antibodies could reasonably be expected. None of the necropsy findings (erythroblastosis, extra-medullary erythropoiesis, or kernicterus) are absolutely pathognomonic of icterus gravis, though they are all highly suggestive.

FAMILY M. The patient, a second child (the first being born normal and now alive and well) had jaundice on the first day, with bile in the urine, and clay-coloured stools. Cholecysto-gastrostomy, performed for fibrous occlusion of the common duct, was followed by recovery. This child was Rh-positive, and its father Rh-positive. Its mother Rh-negative. The mother's serum was not examined for agglutinins at the time of the infant's illness, but they were present in the mother's blood at the third and fourth pregnancies, which resulted in two babies with erythroblastosis foetalis; these died at the age of four and three days respectively, both with kernicterus.

COMMENT. No suggestion has ever been made that this second child in that family was a case of erythroblastosis foetalis. It has been suggested, however, that it was a case of atresia of the common bile duct. Though we do not know all the clinical details, we venture to suggest that the diagnosis of atresia of the bile duct at operation is often difficult to make. To illustrate this point we would like to mention a recent case in which an experienced paediatric surgeon was concerned. This was a patient, aged one month, with obstructive jaundice from the age of four days, and cholecysto-gastrostomy was performed. At necropsy twenty-four hours after operation the bile ducts were patent, and the obstruction was found to be due to liver cirrhosis of obscure nature, Rh incompatibility having been excluded. But assuming that atresia was present in the second child in Family M, there is no reason why congenital atresia of the bile ducts and icterus gravis should not occur in different children of the same family. For these reasons we consider that a direct association was not established in Family M.

The same authors go on to quote a third family of six children, the fourth of which died from congenital obliteration of the bile duct. Its Rh factor was not examined. The sixth child died from erythroblastosis foetalis. Rh antibodies having been present in the mother's blood at the sixth pregnancy. This again appears to be a case of the two conditions, biliary atresia and erythroblastosis, occurring in different children of one family.

We have been unable to find any more reports in the literature of the association of erythroblastosis and congenital atresia, but we now mention a patient who has come under our observation through the courtesy of Dr. Donald Paterson, yet again there was no absolute proof of the association of the two conditions.

M. S., a male baby (two siblings are alive and well and had no neonatal jaundice or anaemia), developed jaundice from the third day which lasted eight days. When six weeks old he had bruising and became anaemic. The jaundice recurred at the age of seven weeks and increased in depth. At eight weeks the liver was found to be enlarged, the spleen was not palpable, and the blood count was 1,500,000 erythrocytes per c.mm. Haemoglobin was 4·8 g. per cent., and two normoblasts were found per 100 white blood cells. The white blood count was 20,600 per c.mm.; van den Bergh 6·7 mg. per 100 c.cm. Urine contained bile pigment. The faeces were very pale. Rh investigations carried out when the baby was nine weeks old showed the baby to be Rh-positive and the mother Rh-negative. No anti-Rh agglutinins were present in the mother's serum. The child was given a blood transfusion of Rh-negative group O blood, and the blood count rose to 5,900,000 erythrocytes per c.mm. When aged four months and still deeply jaundiced, the child was admitted to the Hospital for Sick Children, Great Ormond Street. His blood count was then 5,700,000 per c.mm. (no normoblasts). Haemoglobin was 16·1 g. per cent. The Rh investigations were repeated and confirmed. A laparotomy was performed; the gall-bladder was found to be solid and rubbery and the liver large and cirrhotic, and no bile ducts suitable for anastomosis were found. The child died seven days later at the age of four and a half months. The liver was found to be cirrhotic. Bile plugs were found in the intercellular bile canaliculi. The epithelium of the intrahepatic bile ducts was normal. No extramedullary erythropoiesis was noted. The gall-bladder was small and contained very little white bile. The cystic duct and common bile duct were occluded. The hepatic ducts appeared to be patent but were very narrow. The spleen was much enlarged and showed a marked increase of fibrous tissue.

COMMENT. In this case there was early neonatal jaundice; at two months there was recurrence of the jaundice, which was clinically obstructive in type; there was late onset of a severe anaemia, and later still cirrhosis of the liver and intercellular bile thrombi. Though the mother was Rh-negative and the infant Rh-positive, no evidence of Rh immunization was found in the mother's serum when the infant was nine weeks old; so that in this case of biliary atresia there is again no proof of erythroblastosis foetalis due to Rh incompatibility.

Discussion

The above survey of cases coming under Skelton and Tovey's Type B of biliary obstruction associated with icterus gravis leads us to the conclusion that in no instance has a direct etiological association been proved beyond doubt, though some cases have been highly suggestive of this association.

We have also considered eight cases of atresia of the bile ducts which have been tested in regard to the Rh factor at the Hospital for Sick Children, Great Ormond Street. No evidence of Rh iso-immunization was obtained. The series is very small, but certainly lends no support to the idea that Rh incompatibility is an etiological factor in congenital atresia of the bile ducts.
Biliary Obstruction in Icterus Gravis Neonatorum without Atresia of the Bile Ducts

In this type of biliary obstruction in icterus gravis we include both intrahepatic and extrahepatic obstruction other than atresia of the bile ducts. Skelton and Tovey's Type A, i.e. blockage of one of the larger bile ducts with inspissated bile, is included in this group.

The jaundice of icterus gravis is mainly haemolytic, though an obstructive element is sometimes present as well. When there is obstruction it usually occurs as an evanescent phase, though there have been occasional cases reported in the literature with the period of obstruction lasting for several months. Serological testing has added so much to the accuracy of diagnosis that we propose to confine ourselves to cases which have been reasonably established by Rh investigations. They may show an early onset of an obstructive phase which may be continuous for several weeks or months, or an evanescent phase of haemolytic jaundice with a recurrence of the icterus after a few weeks, and then biliary obstruction, usually partial, lasting for several more weeks. This sequence is illustrated by the following case (Lightwood, 1943).

Case 1. A. C., a male, was a second child. The only sibling, aged four years, was jaundiced for the first three to four days of life, but is now healthy.

Jaundice appeared twenty-four hours after birth and lasted fourteen days; pallor was not noted; the stools were normal. Ten days later, at the age of three and a half weeks, the stools became pale and the urine dark. During the next week the baby became increasingly pale and jaundiced (greenish tinge). One week later still he was seen at hospital with jaundice, anaemia, abdominal distension, prominent veins of the abdominal wall, and ascites (making palpation of the liver and spleen impossible). The stools were pale and the urine dark, and the diagnosis between icterus gravis and congenital atresia of the bile ducts was not easily made. The blood picture did not decide the diagnosis: haemoglobin was 85 per cent., and red blood cells 3,480,000 per c.mm., the colour index 1-3, and white blood cells 22,600 per c.mm. Erythroblastema was not present and would not have been likely to persist so late. The icterus index was 50. The direct van den Bergh reaction was positive, and the indirec reaction 10 units. Wassermann reaction and Kahn reaction of mother and baby were negative. Rh tests, however, showed the baby to be Rh-positive; his mother was Rh-negative, and her blood contained Rh antibody. Therefore the diagnosis of icterus gravis was established.

The infant was gravely ill, and the abdomen needed paracentesis on two occasions, 10 oz. and 20 oz. being withdrawn. The haemoglobin fell to 60 per cent., and an Rh-negative blood transfusion of 150 c.c.m. was given. Thereafter the haemoglobin level was well maintained. Owing to the prolonged jaundice and the presence of such considerable ascites, the prognosis seemed bad, but after paracentesis and blood transfusion the child began to improve. Subsequently he gained weight satisfactorily, and ascites and jaundice slowly disappeared during the next six weeks. This was after an obstructive phase lasting eleven weeks. Even after this there were slight recurrences of obstruction of some two days' duration (two attacks).

Case 2. D. K., a male, aged eleven hours, was admitted to the Hospital for Sick Children, Great Ormond Street, under Dr. W. G. Wyllie, with marked jaundice and hepatosplenomegaly. Birth weight was 7 1/2 lb. The child had asphyxia (the cord was wound twice round the neck), but revived with lobelin.

Two siblings, aged seventeen and fourteen years, were alive and well. The third child of the family died with jaundice at the age of eighteen days. The fourth child miscarried, and the fifth was the patient. On examination, orange-yellow jaundice was noticed, and the liver was palpable three fingers' breadth below the costal margin; the spleen was palpable. Red blood cells were 3,960,000 per c.mm., with 92 normoblasts per 100 white blood cells. The baby was Rh-positive; the mother was Rh-negative, and one week after delivery her serum contained Rh antibody of a titre 1 in 64. At two days old, 205 normoblasts were found per 100 white blood cells. Subsequently the normoblast count decreased gradually. The urine contained bile pigment, and the stools were pale. At one week of age the serum bilirubin was 28-5 mg. per 100 c.cm. At three weeks of age the alkaline plasma phosphatase was 18-4 units per 100 c.cm. (normal 10-20 units). This was taken as an indication against extrahepatic obstruction, and, an indocyanine green test was performed. The obstructive jaundice lasted about four months. When seen, at five months, the infant was feeding and gaining well. The jaundice had completely disappeared, and the van den Bergh reaction in the serum was negative.

The clinical histories just given do not explain the mechanism of obstruction. In contrast, the following cases, coming to necropsy, throw light on the pathology underlying the obstructive phase of erythroblastosis foetalis for they show that at least two states may be found at necropsy, (a) pigment stones, and (b) cirrhosis.

A. Pigment Stones causing Extrahepatic Obstruction

Case 3. A. H., a male, aged four and a half months, came under the care of Dr. Donald Paterson at the Hospital for Sick Children, London. His seven-year-old brother had had no jaundice, but a three-year-old brother had jaundice from the third to the fourteenth day after birth. The patient had had a normal birth (weight 7 lb. 8 oz.), was breast-fed for three days, and had a 'septic' umbilicus until two months old. There was no neonatal jaundice, but jaundice from two and a half months without constitutional disturbances; stools were pale with a yellow tinge, and the urine was dark and contained bile pigment; there was no vomiting, and he was taking his feeds well. When admitted to hospital he had marked jaundice. The liver could be felt one and a half fingers' breadth below the costal margin. The spleen was not felt. Heart and lungs were normal. Red blood cells were 5,120,000 per c.mm. of blood, haemoglobin 110 per cent. (15-5 g. per 100 c.cm.), reticulocytes 1-4 per cent., and there were no nucleated red cells. White blood cells were 14,000 per c.mm. with 69 per cent. lymphocytes. The baby was Rh-positive, the
mother Rh-negative, with anti-Rh agglutinins (titre 1 in 32). The blood Wassermann reaction of the mother was negative. Liver function tests were as follows; van den Bergh, immediate direct positive; quantitative, 8·6 mg. per 100 c.cm. (normal up to 0·5 mg.). Alkaline serum phosphatase was 45·6 units (normal 10 to 20). Takata-Ara reaction was negative.

In view of the obstructive type of jaundice, with a high serum phosphatase and no anaemia, atresia of the bile duct was suspected and reassessment of the case in a further fortnight decided upon. Meanwhile the baby was sent home. More than a week later he was readmitted in extreme dehydration following five days' diarrhoea and vomiting, and died after a few hours. Necropsy showed a wasted, jaundiced infant with moderately enlarged liver and a gall-bladder of normal size. Bile could be squeezed through the common bile duct. Four small dark pigment stones were found in the common bile duct and cystic duct, together with much pigment-sand which was also present in the gall-bladder. There was some dilatation of the bile passages, including the hepatic ducts behind the site of partial obstruction (fig. 1). The portal systems were enlarged, with a moderate increase of reticulin which was dense and stained with van Gieson's mixture (figs. 2 and 3). There was some albuminous degeneration of liver cells. The sinusoids were congested; the bile duct epithelium was normal. An occasional bile thrombus was seen in the intercellular bile canaliculi.

COMMENT. This is a case of erythroblastosis foetalis due to Rh iso-immunization, coming to necropsy during an obstructive phase of jaundice. The obstruction was extrahepatic in nature, due to the presence of bile pigment stones within the larger bile ducts, the liver being comparatively normal. We are not aware of any previous reports of such nature in proved cases of Rh incompatibility, and the tendency to formation of bile pigment stones in this neonatal form of haemolytic jaundice has not received attention.

Pigment stones were also found in another similar case. An infant, aged six months, with a history of jaundice lasting from the second day for five weeks. At six months of age there was no anaemia. The baby was Rh-positive, the mother Rh-negative, with a Rh antibody, titre 1 in 64. The liver was one finger's breadth below the costal margin. The spleen was not palpable. At necropsy the liver was macroscopically and microscopically normal. The gall-bladder was small and contained pale bile and three small pigment stones. The bile passages were patent.

Still, 1927) reported three cases of biliary calculi in infants aged nine months, eight months, and five months respectively, with no history of jaundice in any of them. At the same time he reviewed some twenty cases reported in the literature, and some of these were infants with jaundice, and may have been associated with icterus gravis neonatorum.

In the literature of icterus gravis there are reports referring to obstructive jaundice in newly-born infants being due to inssipated bile within the larger bile ducts (Skelton and Tovey, 1945; Davidsohn, 1945; Ladd, 1935). Moreover, in certain instances surgeons have claimed to have dislodged the obstructing masses by manipulation, but could hardly have been sure of their nature; therefore the tendency to formation of bile-pigment stones in this type of haemolytic disease, as in acholuric jaundice, is of interest. Perhaps after a phase of intrahepatic obstruction with bile plugs within the finer branches of the bile ducts, these plugs become dislodged and pass into the larger bile ducts and form concretions there. Such a mechanism may be responsible in certain cases of prolonged obstructive jaundice in association with erythroblastosis foetalis. There is, however, another mechanism.

B. Cirrhosis causing Intrahepatic Obstruction

Case 4. G. B., a female, aged seven weeks, came under the care of Dr. Donald Paterson at the Hospital for Sick Children, Great Ormond Street, London. This was a third child, one having had erythroblastosis and being alive and well, and one having died from erythroblastosis and pneumonia. The patient had jaundice from birth, and was Rh-positive; the mother was Rh-negative, with Rh antibody, titre 1 in 8; the father was homozygous Rh,Rh. An Rh-negative blood transfusion, 120 c.cm., was given when the child was four days old. Haemoglobin was 98 per cent. before transfusion and dropped to 66 per cent. at 15 days. There was increasing abdominal swelling from the sixth week of life. When admitted to hospital, the child had a swollen abdomen and cyanosis. She was jaundiced, with faint heart sounds and fluid in the abdomen. Red blood cells were 3,540,000 per c.mm., no normoblasts. Yellowish fluid (150 c.cm.) was withdrawn, and subsequently an uneven liver palpated. Another Rh-negative blood transfusion of 70 c.cm. was given, but the infant died three days after admission.

At necropsy there was a good deal of clear yellow free fluid in the abdominal cavity. The liver was large, firm, and greenish-brown, the surface finely granular. Cross section suggested fibrosis. The liver showed marked fatty degeneration and disintegration of liver cells, with perilobular and multicellular cirrhosis. There were many bile thrombi within the intercellular canaliculi, normal bile duct epithelium, and no evidence of erythropoiesis (figs. 4 to 7).

COMMENT. This was a case of Rh iso-immunization with obstructive jaundice of seven weeks' standing, showing cirrhosis of the liver at necropsy with evidence of intrahepatic bile duct obstruction.

Case 5. M. C., a male full-term baby, weighing 7 lb. 14 oz. at birth, left the maternity department of a London hospital on the twelfth day, weighing 7 lb. 8 oz., with no abnormal physical signs. He was readmitted to the hospital at six weeks because he had not gained weight since birth. We could not obtain any history of neonatal jaundice from the mother, but the Rh serology was investigated. The baby was Rh-positive, the father homozygous Rh,Rh, and the mother Rh-negative, with weak anti-Rh agglutinins in serum, titre 1 in 1—but none were present in her milk. At eleven weeks the baby was noticed to be very pale, and a blood count gave the following results: red blood cells 2,540,000 per c.mm.; haemoglobin 46 per cent.; colour index 0-92. The weight was 9 lb. 10 oz. He was given an
FIG. 1—Liver, case 3, showing four pigment stones in dilated common bile duct and cystic duct. (Natural size.)

FIG. 2.—Microphotograph of liver, case 3, showing normal liver pattern and a large portal system with increase in collagen. Stained by van Gieson. (× 90.)

FIG. 3.—Microphotograph of liver, case 3, showing increase in reticulin in portal systems. Silver impregnation stain. (× 60.)
Fig. 4.—Microphotograph of liver, case 4, showing early perilobular cirrhosis and many intercellular bile thrombi. Stained by van Gieson. (× 60.)

Fig. 5.—Microphotograph of liver, case 4, showing increase and condensation of reticulin, particularly in perilobular areas. Silver impregnation stain. (× 60.)

Fig. 6.—Microphotograph of liver, case 4, showing vacuolation (fatty degeneration) and necrosis of liver cells. Many intercellular bile thrombi are present. Stained by haematoxylin and eosin. (× 175.)

Fig. 7.—Microphotograph of liver, case 4, showing a bile duct with normal epithelium in a portal system, surrounded by disintegrated liver columns.
Fig. 8.—Microphotograph of liver, case 5, showing early portal and perilobular cirrhosis, marked vacuolation of liver cells (fatty degeneration), and a number of intercellular bile thrombi. Stained by van Gieson. (× 112.)

Fig. 9.—Microphotograph of liver, case 5, showing increase and condensation of reticulin in portal systems and perilobular areas. Silver impregnation stain. (× 60.)

Fig. 10.—Microphotograph of liver, sibling of case 5, showing fibrous bands with round cell infiltration, surrounding large and small groups of liver cells. Stained by van Gieson. (× 60.)

Fig. 11.—Microphotograph of liver, sibling of case 5, showing increase and condensation of reticulin fibres breaking up liver columns into large and small cell groups. Silver impregnation stain. (× 60.)
iron mixture and did not attend the hospital for about six weeks. At five and a half months he was admitted to the Hospital for Sick Children, Great Ormond Street, under Dr. B. Schlesinger. He was considerably under weight, the liver was firm and enlarged two fingers’ breadth below the costal margin. The spleen was not palpable, and there was no jaundice or oedema. Rh investigations of the former hospital were confirmed. Red blood cells were 4,650,000 per c.mm., and the serum, von den Bergh, and Takata-Ara reactions were negative. Alkaline serum phosphatase was 24-9 units (normal 10 to 20 units). The blood Wassermann reaction was negative.

Three weeks after admission the baby developed a severe middle-ear infection, with diarrhoea and vomiting, jaundice, teleangectases, and small haematemeses, and he died. At necropsy the liver was three fingers’ breadth below the costal margin, firm, with finely granular surface. The gall-bladder was normal. The bile passages were patent throughout. Histology of the liver showed early fibrosis, perilobular, and also round small cell groups. There was marked vacuolation of liver cells. The bile duct epithelium was normal. A fair number of bile plugs were found in the intercellular bile canaliculi, and small bile globulles in liver cells (figs. 8, 9).

Comment. This case of Rh iso-immunization was of interest because at a late stage considerable anaemia developed. Jaundice was not discovered in the early stages. At necropsy, cirrhosis of the liver was found. Another point of interest is the family history, and this is the main reason why the case is included in our series. Siblings were as follows: (1) a miscarriage in 1934; (2) a male child died at three months of ? marasmus in 1935 (? history of dropsy, no further details available); (3) a baby, born in 1939, died at ten weeks of cirrhosis of the liver; (4) the fourth child was the baby whose case is described above.

History of the Third Child

The third child of this family, a female, was jaundiced from the third day for a short time. At seven weeks an obstructive phase of jaundice developed and lasted eight days. A third phase of jaundice developed at nine weeks, with diarrhoea and blood-stained stools, and the infant was admitted to the Hospital for Sick Children, Great Ormond Street, London. Red blood cells were 2,960,000 per c.mm., haemoglobin 60 per cent., blood Wassermann reaction negative. A laparotomy was performed, and a large quantity of free fluid removed. The liver was small and greenish-yellow, and the gall-bladder dilated. The bile ducts were apparently normal. Two days later the operation findings were confirmed at necropsy. Histology of the liver showed intense multicellular fibrosis with numerous intercellular bile thrombi. The epithelium of the bile ducts was normal.

This baby must have been Rh-positive, since her father was homozygous Rh-positive. No test was made for Rh agglutinins in the mother’s serum (in 1939) but it is reasonable to assume that the third infant was a case of Rh iso-immunization, as was the fourth child (case 5 above), and that this led to liver cirrhosis in both cases. The intermittent obstructive jaundice is another interesting feature in this case.

Discussion

The fundamental work on iso-immunization in erythroblastosis has taken us far on the road to full understanding of this disease, but understanding will not be complete until a number of clinical and pathological facts have been correlated. For instance, why should the clinical symptoms occasionally make their first appearance as late as the third or fourth week after birth? Why should the jaundice sometimes persist for several weeks or even months? In erythroblastosis the haematology has been intensively studied, but the pathology of the liver has received insufficient attention; haemopoiesis has been generally noted, but little attention has been given to the changes which can often be seen in the liver cells. In early cases of icterus gravis, Hawksley and Lightwood (1934) showed the possibility of considerable necrosis in the polygonal cells, and that hepatic cirrhosis may follow at a later stage. These observations were confirmed by Henderson (1942), who found even greater changes in stillborn erythroblastic foetuses, and by Gilmour (1944).

The condition of the bile ducts in erythroblastosis has also received too little attention. On clinical grounds the jaundice has been regarded as purely haemolytic. In icterus gravis the stools are usually well-coloured and bile pigment is often excessive. Hawksley and Lightwood (1934) accepted the haemolytic mechanism, but showed that there could be an evanescent obstructive phase as well. Thus it became necessary to recognize two mechanisms, haemolytic and obstructive (Ross and Waugh, 1936), and haemolysis is the factor chiefly concerned.

Biliary obstruction may occur at the height of the haemolytic jaundice or may only appear two to four weeks afterwards. The icterus is never wholly obstructive unless a late stage is reached. It is when the phase of obstruction is prolonged that confusion with congenital obliteration of the bile ducts is likely (Lightwood, 1943). Both conditions may show clinical remissions. Anaemia is often present in cases of atresia of the bile ducts, and we have seen counts of 3,000,000 red cells per c.mm.; in one case (M. S., see p. 2) the red count was 1,500,000 per c.mm. The presence or absence of bile in urine and stools are certainly not distinguishing features: we have seen cases of icterus gravis in which stercobilin was absent from stools. The alkaline serum phosphatase may be of critical value. A normal value is evidence against extrahepatic obstruction. The degree of rise in phosphatase does not, however, help in differentiating intrahepatic from extrahepatic obstruction: we have seen values of some 40 units in atresia of the bile ducts, and of some 80 units in cirrhosis of the liver with patent main bile ducts. On the other hand, low values may be found in cirrhosis and higher figures in atresia.

The data in the present paper suggest that biliary obstruction may appear as early as the first week in cases of erythroblastosis, or later, and that, once established, this type of icterus may continue for several months, or pursue a recurrent course.

In our fatal cases we have observed varying
degrees of albuminous degeneration, fatty degeneration, and focal or diffuse necrosis of liver cells. Increase of reticulin was noted in all the fatal cases. In some it was most marked in the portal systems, which were enlarged. In other cases reticulin was particularly increased in the periphery of the lobules, but also around small groups of cells. Where reticulin fibrils were condensed, they could be stained with van Gieson's mixture. We have deliberately looked for histological evidence to indicate that the lining epithelium of the bile ducts can be damaged or structurally altered in icterus gravis, for example by an antigen-antibody reaction in the neighbourhood, or by stagnation of bile in their lumina. No such evidence has been seen. In a few cases we have found that the obstruction is extrahepatic through the presence of pigment stones in the larger ducts.

In icterus gravis, where there is prolonged biliary obstruction, the clinical picture closely resembles congenital atresia, and it is natural that a causal relation has been suggested by more than one observer, but we have been unable to obtain any wholly satisfactory evidence of any such cause and effect. Although there are records of suggestive cases, we find that the evidence to date does not indicate a true association.

While an obstructive jaundice persists, the prognosis remains in doubt though it is by no means necessarily bad. In favourable cases the jaundice eventually clears, but in others cirrhosis occurs.

Our findings in case 5 and sibling suggest another etiological factor for familial cirrhosis of the liver.

Summary

The first part of the paper contains a review of the literature of cases of biliary atresia thought to be causally associated with icterus gravis neonatorum. In the light of Rh serology, no such association appears to have been proved beyond doubt, though some cases are highly suggestive. At any rate, Rh iso-immunization would not appear to be a major etiological factor in the pathogenesis of atresia of bile ducts.

In the second part of the paper, specimen cases are reported illustrating the intermittent and the continuous obstructive type of jaundice occurring in icterus gravis. This is followed by case and necropsy reports indicating the pathology underlying obstructive jaundice in icterus gravis: intrahepatic obstruction due to liver-cell damage which may lead to cirrhosis of liver, or extrahepatic obstruction due to pigment stones in the main bile ducts. The diagnosis between these two conditions and atresia of the bile ducts is discussed.

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