ERYTHROBLASTOSIS FOETALIS

Part III

BY

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Erythroblastosis foetalis type I (hydrops foetalis) and type II (icterus gravis) have been described in parts I and II, p. 1 and 12.

Type III. Congenital anaemia (two cases)

Maternal and obstetric history, age and sex. An earlier child of the mother in one case died in infancy, but the cause of death was not recorded. No information was available about the mother in the other case. The body lengths were 51 and 52 cm. and both subjects were probably mature. One was male, the other female. One died on the eleventh day, the other on the twelfth.

From accounts in the literature it was apparent that, in contrast to hydrops foetalis and icterus gravis, the incidence of miscarriages, stillbirths and deaths in the first days of life without obvious erythroblastosis was not great in families in which infants with congenital anaemia occurred. Seven instances of a familial incidence of congenital anaemia have been recorded. Instances of erythroblastosis, types I or II, in twins or siblings of infants with type III will be mentioned later. In thirty-six cases in the literature there were fifteen males and twenty-one females. It is doubtful whether this predominance in females is of significance. Most infants were apparently full term. Of forty-six reported cases eleven were fatal. Death occurred between the fourth and thirteenth days inclusive. The subjects in the remainder recovered with or without treatment.

Clinical history. The infant in one case was normal till the fifth day when it became pale and slightly jaundiced. Jaundice had disappeared by the time of death. The other showed from birth slight jaundice and increasing pallor. In both death was due to anaemia.

In thirty-nine reported cases pallor was noted at birth in eleven and appeared in the first seventeen days in the remainder. Jaundice was present in fifteen of forty-two cases, in two at birth. In the case of Cohen (1935) the vernix caseosa and liquor amni were orange coloured. In some cases the jaundice was severe in the first days of life and then subsided or disappeared leaving marked pallor. Usually the jaundice was mild throughout. Anaemia was constant; it was usually moderate, but in

twelve cases the erythrocytes fell below one million per c.mm. In a few cases, as described by Segar and Stoeffler (1932), Bonar and Smith (1933), Abbott and Abbott (1935), and Bernheim-Karrer (1936-7), the erythrocytes in the first days of life were over four million per c.mm., and this slight anaemia was unaccompanied by excess of erythroblasts in the blood, but later became severe. Erythroblasts were usually present, and occasionally in large numbers. They were absent in the cases of Åkerrén (1932-3) and Parsons, Hawksley, and Gittins (1933). In the cases of Frank (1926), Gelston and Sappington (1930), Bonar and Smith (1933), and Snell (1938) they did not appear till the thirteenth day or later. Buchan and M'Gibbon (1906) and Abt (1932) described basophil erythroblasts (primary erythroblasts) in the blood and Abt (1932) and Otaway (Diamond, Blackfan, and Baty, 1932) found erythrophages. Reticulocytosis was reported by some authors and leucocytosis by many. Marked leucocytosis, as in the case of Youland (1929), was usually associated with myelocytes. The van den Bergh test in the few cases in which it was performed gave a higher indirect positive reaction than normally. The course of the anaemia varied. In some it was mild and recovery occurred with or without treatment. In others it was more severe, but the subjects recovered on treatment with transfusions. Recovery was often slow. Buchan and M'Gibbon (1906) and Parsons, Hawksley and Gittins (1933) described prolonged cases in which the anaemia began to resemble that of von Jaksch. In other cases there was no response to treatment and the anaemia progressed with little sign of regeneration of the blood. In these cases death occurred within the first fortnight. Slight localized oedema, such as of the scrotum, appeared in a few cases during the illness and in a case of Boehncke (1938-9) it became generalized. Haemorrhages were not a feature of the disease, but in a few cases petechiae appeared in the skin. In most cases the spleen was palpable during the greater part of the illness.

Macroscopic appearances at necropsy. The most conspicuous finding was marked pallor of the skin, muscles, and internal organs. In one case there was very slight jaundice of the skin, conjunctiva, aortic intima, lungs and kidneys. Petechial haemorrhages were present in the visceral pleura in both cases, and in the tentorium cerebelli and superior mediastinum

in one. In one case there were slight effusions in the coelomic cavities, the largest being 1 ounce, and peritoneal; the spleen was enlarged and there was slight bronchopneumonia.

The information given in reported fatal cases was very scanty. Pallor was mentioned in all, and jaundice, splenomegaly, or multiple small haemorrhages in some.

Weights of body and organs. The weights of the body, thymus and heart were within the normal limits. In one the weight of the spleen (35 gm.) was above the maximum normal and the liver weight was very high (227 gm.), but not above the maximum normal for full-term infants at birth.

Microscopical appearances

HAEMOPOIESIS. In both cases there was a paucity of erythrocytes in the tissues examined. In one case excessive haemopoiesis of the liver was slight, chiefly leucopoietic, and shown by a few small groups of cells and diffusely scattered cells, most of which were in sinusoids. The predominant cell was the haemocytoblast, but there were many myelocytes and fewer leucocytes. Primary erythroblasts were scanty, normoblasts very scanty and megaloblasts absent. There were a very few megakaryocytes. In the spleen in this case haemopoiesis was also excessive and chiefly leucopoietic and shown by a diffuse infiltration with promyelocytes, myelocytes and leucocytes and many small groups of haemocytoblasts, while primary erythroblasts and normoblasts were very scanty and megaloblasts and megakaryocytes absent. In a kidney there was a small group of haemocytoblasts and early primary erythroblasts; erythropoiesis of this character is

FIG. 17.—Congenital anaemia. Marrow of femur. Increase of megakaryocytes. Haem. and eosin. $\times 200$.

abnormal in this site. In the mesenteric, iliac and cervical lymph glands there was excessive leucopoiesis and, in a cervical gland, a megakaryocyte. In the haemopoietic marrow of a femur there was evidence of hyperplasia in that haemocytoblasts, myelocytes and megakaryocytes (fig. 17) were relatively more abundant than normally. There were foci of primary erythroblasts of all stages, but secondary erythroblasts, consisting of normoblasts and late megaloblasts, were very scanty. In the other case haemopoiesis was slightly excessive in the liver (fig. 18). There was leucopoiesis in the portal

FIG. 18.—Congenital anaemia. Liver. Excessive amount of haemopoiesis. Haem. and eosin. $\times 155$.

systems, and within the lobules a slight diffuse scattering of haemopoietic cells chiefly within the sinusoids. Haemocytoblasts predominated and promyelocytes, myelocytes and leucocytes were in about equal number to the erythroblasts so that leucopoiesis was relatively increased. Most erythroblasts were primary, but a few were normoblasts or late megaloblasts. One megakaryocyte was seen. In the spleen haemopoiesis was markedly excessive and the Malpighian bodies were obscured (fig. 19). There was as much leucopoiesis as erythropoiesis. Among the erythroblasts normoblasts were few and megaloblasts absent. There were no megakaryocytes. A lung showed a focus of leucopoiesis in the peribronchial tissue. In the marrow of a rib haemocytoblasts appeared unusually numerous.

In ten cases reported with necropsies in the literature there was excessive haemopoiesis in the liver and spleen in all and in some other tissues in a few. In the cases of Pasachoff and Wilson (1931), Abbott and Abbott (1935), and Tow (1937) it was chiefly leucopoietic and poor in erythroblasts. This, as in my cases, was significant of a hold up in the development of the erythron.

OTHER TISSUES. In both cases there was haemosiderosis of the hepatic cells. In one there was

fatty degeneration of the hepatic cells while in the other they showed albuminous degeneration and those near some of the centres of the lobules were dropsical. The Kupffer cells were large, conspicuous and contained much diffuse or globular iron pigment. This, and the number of erythrophages was not abnormal. Haemosiderosis of the spleen was shown in both cases by diffuse, granular or globular haemosiderin in very numerous reticulum cells and fewer sinus cells. In one the capsule and trabeculae showed a few small patches of iron impregnation which stained deeply with Ehrlich's haematoxylin. In a rib in one case the zone of provisional calcification of cartilage was normal, but the adjacent metaphysis showed unusually numerous trabeculae of calcified cartilage upon which only shallow seams of bone, or in places no bone at all, had been laid down. This change was commonly found in hydrops foetalis.

Differential diagnosis

Congenital syphilis. Anaemia is not uncommon in congenital syphilis, and Stuhl (1906) and Alexandrowski (1916) have reported cases in which it was very marked and not unlike that in congenital anaemia.

Other forms of anaemia in the newly born. Anaemia may follow pyogenic infections, but the relationship between the infection and anaemia should easily be recognized clinically. It is usually mild and not associated with jaundice, a familial history, marked erythroblastaemia or a lack of regeneration of the blood. An excess of megakaryocytes in the marrow, such as occurred in some of the cases of congenital syphilis already described, has been reported in the literature in anaemia following sepsis, but it was found also in one of the cases of congenital anaemia.

Anaemia, such as the anaemia of prematurity, may be due to iron deficiency. It is mild and hypochromic and associated with maternal anaemia, but not with a marked erythroblastaemia or a lack of regeneration of the blood or with jaundice, except possibly icterus neonatorum.

Definition of type III

Type III (congenital anaemia) is found in infants which always survive the first three days, and is shown by pallor and anaemia which are present at birth or appear in the first three weeks. Jaundice is common, but relatively mild, and oedema is always absent at birth and usually absent later. There is no change peculiar to the type and not found in other diseases. No change is constant except anaemia. The definition is based upon the exclusion of other forms of neonatal anaemia and the presence of one or more of the following characteristic but inconstant features: a familial history; excessive haemopoiesis, erythroblastaemia and leucocytosis or, in infants

dying between the third and fourteenth days, a defective development of the later stages of the erythron and the absence of erythroblastaemia; splenomegaly; haemosiderosis of the liver.

Type III differs from I chiefly in that in the latter death is the rule and occurs in utero or within the first thirty-six hours and general oedema and lipid infiltration of the suprarenal cortex are usually

FIG. 19.—Congenital anaemia. Spleen. Excessive amount of haemopoiesis. Haem. and eosin. $\times 250$.

present. Type III differs from II in that pallor is marked compared with the mildness of the jaundice in type II and cerebral jaundice does not occur.

Discussion of erythroblastosis

Evidence of the identity of the nature of the disease in the three types is shown by the frequent presence of more than one type in different members of the same family and by certain common clinical and pathological features. The differences between the types probably depend chiefly upon differences in the severity of the disease and the age at its onset.

The occurrence of icterus gravis in one or more siblings and of hydrops foetalis in another or others has been described by Seulen (1835), Smith (1875), King (1908), Plaut (1927), Bock (1930), Salomonsen (1931), Diamond, Blackfan, and Baty (1932), de Lange (1932), and Wolfe and Neigus (1940). De Lange (1932) described icterus gravis in one twin and hydrops foetalis in the other. The occurrence of icterus gravis in one or more siblings and of congenital anaemia in another or others has been described by Diamond, Blackfan and Baty (1932), de Lange (1934), Abbott and Abbott (1935), Bernheim-Karrer (1936-7), Wolfe and Neigus (1940) and, in one particular family, by Buchan and M'Gibbon (1906), Buchan and Comrie (1909) and M'Gibbon (1912-13). Wolfe and Neigus (1940) reported congenital anaemia in one twin and icterus gravis in the other. Pasachoff and Wilson (1931, 1935) described congenital anaemia in one infant and hydrops foetalis in two siblings born later.

Clinically erythroblastosis of type II occasionally passes into type III with lessening or disappearance of the jaundice and increase of pallor.

Pathological similarities between the types are as follows: Jaundice sometimes occurred in type I and III, although seldom in type I. Oedema and effusions were usual in type I, but occasionally occurred in a lesser degree in the other types. An abnormality in haemopoiesis, with anaemia and excessive blood formation in the liver and other tissues was present in all cases of type III and in most cases in the other types. Haemosiderosis of the liver was very common in all types. The capsule and trabeculae of the spleen in some cases of all types showed iron impregnation. Splenomegaly was very common in all types. An abnormality in endochondral ossification was very common in type I, it was present in one case of type III and there was evidence that it occurred in two cases of type II reported in the literature. Increase of reticulin or fibrosis in the liver was common in type I and it occurred in a few cases in type II.

Little need be said here concerning the etiology. The familial incidence shows that the disease depends upon an hereditary factor. The effect of this is chiefly upon the hepatic and haemopoietic tissues. The effect on the liver was shown by either areas of necrosis or loss of hepatic cells, increase of reticulin or frank diffuse fibrosis, retention of bile in intercellular canaliculi or in liver cells, or possibly fatty degeneration. Fatty degeneration is a change commonly found in anaemia, but in one case of type I and four of type II it was not associated with apparent anaemia or histological evidence of abnormal haemopoiesis. In three of these four cases of type II, however, haemosiderosis of the liver suggested that anaemia had been present or that it was unaccompanied by regenerative hyperplasia of primitive blood cells. The fatty degeneration of the liver in one case of type III and the albuminous and dropsical degenerations in the other might well have been due to the anaemia present. One or more of the changes mentioned above, excluding fatty degeneration, was present in ten of thirteen non-macerated cases of type I, all twenty-five cases of type II, but in neither of the two cases of type III. In the ten cases of type I there was an increase of reticulin which amounted to a diffuse fibrosis in two. It was associated with proliferation of pseudobile canaliculi in five and bile thrombi in intercellular canaliculi in seven, in five of which bile was also present in hepatic cells. In twenty of the twenty-five cases of type II in which the liver was examined there were bile thrombi in intercellular canaliculi. The thrombi were associated with bile in hepatic cells in twelve, with foci of loss of hepatic cells in one, foci of necrosis or of loss of hepatic cells in two, and an increase of reticulin in two; in one of these two there was also fibrosis of the portal systems. In the five cases without bile thrombi there were foci of necrosis of hepatic cells in one and an increase of reticulin in another, but four showed fatty and one albuminous degeneration. The jaundice in many cases was undoubtedly toxic, that is to say, due to hepatic damage. This was shown by a biphasic van den Bergh reaction being usual in type II, and by the presence of bile in intercellular

canaliculi or in hepatic cells in some cases of types I and II. There are no reported data concerning the van den Bergh test in type I. Accumulation of bile in the liver is not a change recognized in cases of jaundice of definitely haemolytic origin. It occurred in all the non-macerated cases of type I in which there was macroscopic jaundice and in all but five of twenty-five cases of type II; in the remaining five cases one or more of the other hepatic changes mentioned above were present. In cases of type III with jaundice the van den Bergh reactions reported have been indirectly positive alone; such a reaction occurs in jaundice of definitely haemolytic origin, but would be expected in mild toxic jaundice if the liver cells were less able than normally to liberate free bile pigment from that combined with protein.

The effect upon haemopoiesis was shown chiefly by anaemia, excessive numbers of erythroblasts in the blood, haemosiderosis of the liver and excess of haemopoietic tissue. In three cases of type II haemosiderosis was present without signs of an abnormality of haemopoiesis, but such an abnormality might have been present earlier in the illness. One case of type I and another of type II showed no evidence that haemopoiesis was or had been abnormal. Blood counts would have demonstrated normality more accurately than histology, there are reports in the literature of normal blood counts in a few cases of type II. The disturbance of haemopoiesis varied in different cases both in my series and in the literature, not only in gravity but in character. Consequently the resulting anaemia was in some cases megaloblastic, in others normoblastic and in others leuco-erythroblastic, leucocytosis being associated with haemocyto blasts and myelocytes in the blood. It was sometimes accompanied by marked regeneration, as shown by an excessive amount of haemopoietic tissue and a marked erythroblastemia; in a few cases of type II regeneration had corrected the anaemia, but erythroblastemia persisted. In other cases, especially fatal cases of congenital anaemia, there was a defective development of the later stages of the erythron and no excess of erythroblasts in the blood. This lack of regeneration probably resulted from exhaustion of hyperplastic haemopoietic tissue and was not the primary cause of the anaemia.

Weiner, Levine, Landsteiner, and others (Levine, 1941) showed that most cases of erythroblastosis depend upon the Rhesus or Rh factor. This is an agglutinin, independent of other agglutinogens, which is present in the blood of 86 per cent. of the population, but in only 8 per cent. of mothers of infants with erythroblastosis. They suggest that the foetus inherits the factor from a Rh-positive father and that a Rh-negative mother is immunized by the foetal blood, anti-Rh bodies being formed within her blood. These antibodies are presumed to filter through into the foetus and cause haemolysis. Other group differences have been found to explain erythroblastosis in infants of Rh-positive mothers. To explain a few cases recorded in the literature in which anaemia was absent or slight shortly after

birth as shown by erythrocyte counts of over four million per c.mm. and absence of erythroblastæmia, but in which typical congenital anaemia developed later, it would be necessary to postulate either an increased titre of antibody in the mother after delivery and a transmission by the milk, or a greater facility of transmission by the milk than by the placenta. Boorman et al (1942) have noted that the titre is low soon after delivery but rises to a maximum between seven and twenty-one days later. Regeneration of the blood with reticulocytosis and erythroblastæmia, haemosiderosis of the liver, and in many cases an indirect van den Bergh reaction suggest that the anaemia of erythroblastosis is haemolytic. A relationship between erythroblastosis foetalis and Rh or other group differences between the mother and foetus is proved and the differences could account for the anaemia. The alteration in bile formation and the cellular damage present in the liver in many cases could be explained as an effect of the union of anti-Rh bodies from the blood and Rh fixed to hepatic cells. The cerebral changes possibly have a similar cause but, as has been mentioned with the description of these changes, they might be secondary to hepatic disease. Localization of Rh in ganglion cells might explain the degeneration or necrosis of these cells in nuclear jaundice, whereas localization in the walls of vessels might account for the focal necroses observed in some cases of icterus gravis. Cerebral jaundice is probably due to an increase of permeability of capillary walls secondary to the cellular damage in the brain. It does not appear possible at the present time to ascribe the general oedema, lipoid infiltration of the suprarenal cortex and increase in size and number of islets of Langerhans observed in hydrops foetalis to a direct effect of Rh or other group differences between the mother and foetus. The erythroblastosis that may occur in association with congenital syphilis or diseases leading to mechanical interference with the circulation is possibly also due to group differences but the serological aspect of such cases has not been investigated. It is known that erythroblastosis appears in a proportion only of Rh-positive foetuses whose Rh-negative mothers contain in their blood anti-Rh bodies. By increasing the permeability of the placenta to Rh and Rh-antibodies these diseases could increase the incidence of erythroblastosis.

Summary

Fifty-two fatal cases of erythroblastosis foetalis have been examined, particularly from the aspect of morbid anatomy. They have been grouped into three types. These correspond to those recognized as hydrops foetalis, icterus gravis and congenital anaemia, but they include a few atypical cases in which the change giving the name to the type is slight or absent. Evidence that the three types are merely varieties of a single disease is given by refer-

ence to the frequent occurrence of more than one type in siblings. The pathological changes have been described and compared with those recorded in the literature. The changes were variable in incidence and degree and none was found constantly. Lipoid infiltration of the suprarenal cortex was common in type I and does not appear to occur in other diseases. Nuclear jaundice and jaundice of the renal medullary pyramids, and foci of necrosis of the white matter occurred in type II and have been found in no other disease. When these changes were absent the acceptance of any case as an instance of the disease and of one of its types depended upon the presence of other inconstant features and the exclusion of other diseases which may produce them. The cause of erythroblastosis foetalis is discussed.

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