NEONATAL APLASTIC ANAEMIA AND FANCONI'S ANAEMIA

BY

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This report is concerned with two cases, a mother and her daughter. The mother was born with a dislocated hip and during childhood developed a hypoplastic anaemia, from which she recovered after the onset of puberty, having previously received a series of blood transfusions. During her first pregnancy she was found to have antibodies to the D antigen and these resulted in severe haemolytic disease in her child. From this the baby recovered, only to succumb to a rapidly progressive marrow failure that resulted in death at the age of 12 weeks.

Case Reports

Case 1. The mother was born on July 25, 1936, and first came under hospital care during infancy because of a congenital dislocation of the left hip. This was treated by immobilization and, later, open reduction. At the age of 10 years she was under the care of Dr. T. E. Gumpert who diagnosed maturation type aplastic anaemia. This failed to respond to haematinics and the only useful treatment was blood transfusion which was repeated at intervals over the next two years. A marrow biopsy before one of the transfusions was reported by Dr. E. K. Blackburn as showing hypoplasia of the three main elements, and he considered the diagnosis to be a primary refractory anaemia of macrocytic type. The platelet count at this time was only 21,000/c.mm.

The last blood transfusion was given in September 1949, and this raised the haemoglobin from 46% (6.8 g. %) to 86% (12.6 g. %). Thereafter no further transfusions were necessary. This spontaneous improvement coincided with the menarche. She became pregnant in 1960 for the first time, and at her first antenatal visit at 13 weeks' gestation her haemoglobin was 90% (13.3 g. %). She was group O Rh negative (cde/cde), but no atypical antibodies were found. Repeat tests at 34 and 36 weeks, however, showed the presence of immune anti-D. Her husband's blood group is O Rh positive (CDe/CDe). She developed pre-eclampsia and a caesarean section was performed at 37 weeks. Ten days after delivery, the blood findings were: haemoglobin 64% (9.4 g. %); colour index 1.0; R.B.C. 3,140,000/c.mm.; W.B.C. 5,000/c.mm. (neutrophils 64%,

eosinophils 1%, lymphocytes 31%, monocytes 4%); platelets 105,000/c.mm. Platelet antibodies at this time were absent, but eight months later the serum was found to contain a platelet antibody titre of 1:4 and also a leucoagglutinin in undiluted serum (Dr. D. Nelken).

Case 2. The first child of Case 1 was born on August 12, 1960. She was limp and pale at birth and did not breathe for 10 minutes. At 1 hour she looked moribund. There were no signs of movement apart from feeble respiratory efforts with occasional grunting respirations. Pallor was extreme and she felt cold to the touch despite having been in a warm incubator since birth. There was no jaundice, but she had numerous scattered petechiae and ecchymoses which were particularly marked on the soles of both feet. She had slight pitting oedema of the legs, an enlarged liver (three fingers' breadth below the right costal margin) and a slightly enlarged spleen (one finger's breadth). She was in fact what we have termed a prehydropic baby (O'Neill and Gordon, 1959). The cord blood findings were Coombs test positive, blood group O Rh positive, haemoglobin 30% (4.4 g. %) and bilirubin 3.0 mg./100 ml.

An exchange transfusion was indicated and because the baby was in heart failure this was done by the extended method (O'Neill and Gordon, 1959). It was started two and a half hours after birth at which time a further venous sample showed the haemoglobin to be only 25% (3.7 g. %). Partly packed group O Rh negative blood was used and the transfusion was extended for 13 hours during which time the venous pressure came down to normal and the liver receded to one finger below the costal margin as the baby came out of heart failure. At 24 hours old she was a normal looking warm pink baby. The purpura was still present at this time, but was less obvious because the baby was now pink, and there was no increase in the number of purpuric spots.

During the following four days the baby's behaviour was perfectly normal. The haemoglobin varied between 100% (14.8 g. %) and 116% (17.2 g. %) and the serum bilirubin never rose above 3.0 mg./100 ml. Thus recovery from the haemolytic disease was perfectly satisfactory. However, on the fifth day of life she had a slight bleed from the oral mucosa followed by severe haematuria

which was prolonged over two days. During the same time she developed fresh crops of purpura and her haemoglobin fell to 60% (8.8 g. %), this presumably being secondary to the bleeding. However, without further clinical evidence of bleeding the haemoglobin fell still further to 40% (5.9 g. %) and a simple transfusion of group O Rh negative blood was given on the fourteenth day of life.

At the onset of bleeding on the fifth day further blood studies revealed a platelet count of only 25,000/c.mm. The white blood count was 8,000 per c.mm. with a normal differential count. In view of the thrombocytopenia the baby was treated with prednisolone, 3 mg. per day. This dosage was later increased to 10 mg. per day with no effect and it was eventually stopped.

It can be seen from the Figure that repeated transfusions were required at intervals of approximately 10 days. The fall in haemoglobin on each occasion was preceded by clinical evidence of bleeding (purpura, epistaxes and/or melaena) and was associated with a drop in the platelet count. On all but two occasions the baby was transfused with platelet-rich blood in an attempt to raise the platelet count to less dangerous levels.

A marrow biopsy taken when the baby was 39 days old showed moderate cellularity, mainly due to cells of the myeloid series, with depression of the erythron and absence of megakaryocytes. The marrow differential count is shown in the Table.

On November 1, 1960, the baby became pyrexial and fretful and refused feeds, but the only signs of infection were a small scalp abscess and blepharitis. However, a white blood count showed severe neutropenia (white blood count 1,400/c.mm. with 2% neutrophils, 2% band cells, 2% plasmacytes and 94% lymphocytes) and despite treatment with penicillin, streptomycin and erythromycin she died five days later at the age of 12 weeks.

Autopsy (Dr. A. J. N. Warrack). Autopsy revealed bronchopneumonia and a small organizing occipital lobe haemorrhage. Sections of a rib and femur showed a somewhat hypocellular marrow in which immature granulocytes (myelocytes) were predominant, nucleated red cells forming a small minority only. Megakaryocytes were very sparse. Iron-laden histiocytes were prominent.

Discussion

The first case, the mother, had an illness similar to that described by Fanconi (1927). The second case, her child, had severe erythroblastosis foetalis followed by thrombocytopenia heralding the onset of fatal aplastic anaemia.

Her condition differed from that of her mother's and most other cases of Fanconi's syndrome in that she had no associated congenital abnormalities (Estren and Dameshek, 1947), and the anaemia was manifest shortly after birth. However, both mother and child did have aplastic anaemia and it seems unlikely that this association was fortuitous. The

FIGURE.—Case 2: platelet and haemoglobin values.

baby's illness was complicated by preceding Rh incompatibility, and this aspect is now discussed.

Erythroblastosis Foetalis. During her prolonged aplastic crisis the mother was given numerous transfusions with what was described as compatible group O Rh negative blood and, although they were looked for in early pregnancy, antibodies (anti-D) were not detected until the 34th week. The development of Rh antibodies without previous sensitization and in sufficient quantity to cause severe haemolytic disease in a first baby is extremely rare, and the more likely explanation is that the mother on one occasion was inadvertently transfused with Rh positive blood.

TABLE
MARROW DIFFERENTIAL COUNT

Cells	%
Neutrophils, segmented	4.75
band	3.88
metamyelocytes	15.75
myelocytes	13.75
semi-mature myelocytes	3.63
promyelocytes	2.0
Eosinophils, mature	2.63
metamyelocytes	0.63
myelocytes	1.0
Basophils, mature	0.5
Myeloblasts	0.5
Monocytes	6.13
Promonocytes	0.5
Lymphocytes	32.6
Normoblasts, orthochromatic	0.5
polychromatic	7.87
basophilic	1.5
Pronormoblasts	0.5
Haemocytoblasts	0.13
Reticulum cells, macrophage and endothelial	0.25
plasma cells	1.0
Total	100

L/E ratio 3.5 : 1.

The baby was delivered three weeks before term, yet was very severely affected by haemolytic disease of the newborn. There was no reason to doubt that Rhesus incompatibility was the cause of the baby's severe initial illness, and response to treatment was excellent. That purpura was present at birth is not surprising as this is a well-recognized complication of severe Rhesus incompatibility. According to Stefanini, Mednicoff and Plitman (1954) the thrombocytopenia that results in purpura in these babies is almost certainly immunological in origin, and this suggestion is supported by their finding of platelet agglutinins in some cases. However, as they point out, exchange transfusion usually results in a prompt rise in the platelet count so that further bleeding is not expected. Case 2 followed the usual pattern exactly up to the fifth day, but then started to bleed again. At this time the platelet count was only 25,000/c.mm., but the haemoglobin was 84% (12.4 g. %) and the white blood count 8,000/c.mm. with 52% neutrophils. The second stage of the baby's illness, therefore, resembled very closely the condition of neonatal thrombocytopenia caused by passage of platelet agglutinins across the placental barrier. If this had been so the prognosis would have been good because few of these cases succumb to serious bleeding, and the transferred antibody gradually lessens so that the platelet count rises spontaneously to normal, usually within one to 15 weeks of life (Stefanini and Dameshek, 1955). Instead of showing improvement, however, Case 2 gradually proceeded to marrow failure that resulted in death at the age of 12 weeks.

That severe erythroblastosis foetalis can result in secondary depression of the erythron, which is in excess of the normal physiological aregenerative phase, is well documented (Diamond, 1948; Smith, 1949 and Gasser, 1957), although there are those who do not support this view (Gairdner, 1958). No mention could be found of erythron depression secondary to haemolytic disease of the newborn of the degree found in our case, neither was there reference to involvement of all three marrow elements. However, there is good evidence of foetomaternal leucocyte and platelet incompatibility (Payne and Rolfs, 1958; Stefanini and Dameshek, 1955) with transfer of antibodies across the placenta, probably by a mechanism similar to that operating in Rhesus incompatibility. Thus it seems reasonable

to suggest that anti-leucocyte and anti-platelet antibodies, as well as those active against red cells, could depress the baby's marrow and so result in a picture similar to that of Case 2. Presumably such antibodies could have been produced in the mother following sensitization by incompatible blood. The other possibility is that they were present in the mother before she was transfused. In support of this theory is the work of Nelken, Gurevitch and Gilboa-Garber (1961) who have recently demonstrated antibodies to red cells, white cells and platelets in cases of pancytopenia.

Summary

Two cases, a mother and her daughter, are described. The mother had a congenitally dislocated hip and during childhood developed aplastic anaemia from which she went into remission. The daughter had severe haemolytic disease at birth and died of marrow failure at 12 weeks of age.

It is suggested that the mother's illness is a *forme fruste* of Fanconi's syndrome and that the baby's marrow failure was the result of placental transfer of antibodies that were present in the mother before her blood transfusions (one of which sensitized her to D) or else were associated with the anti-D and persisted to cause the infant's death.

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