The results are discussed and are considered to indicate that erythrocytic malaria in Gambian children exerts its main effects in the first two years of life, chiefly through the clinical illness produced by the acute attack. Malarious children, once they have acquired sufficient resistance to the noxious effects of clinical malaria, appear rapidly to make good lost ground despite the persistence of moderately dense parasitaemia. A consistent relationship between hepatomegaly and erythrocytic malaria is defined. The view is expressed that the serum protein changes observed in malarious children may in part be due to the formation of humoral antibodies.

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STUDY OF TRANSFUSED PLATELETS IN A CASE OF CONGENITAL HYPOPLASTIC THROMBOCYTOPENIA

BY

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The following case of neonatal thrombocytopenia is of interest because of the rarity of the haematological disorder, which was apparently a primary aplasia of the megakaryocytes associated with a congenital skeletal defect of the forearms, and also because it was possible to give relatively large transfusions of platelets in view of the recipient's small blood volume. In the virtual absence of platelet production in the infant, the effectiveness and survival of these transfused platelets could be readily studied.

Case History

This child, a female, was born at term of the mother's second pregnancy. Its weight was 6 lb. 2 oz. (2,780 g.). The first pregnancy had miscarried at two months. Vaginal bleeding had occurred also in this pregnancy during the twelfth week. No consanguinity existed between the parents, who were in good health.

The infant was born with a deformity of both arms, due to the absence of both radii, resulting in diminutive forearms with abducted hands, but otherwise appeared healthy.

Progress was uneventful until the sixth week, when melaena occurred, immediately followed by the appearance of scattered petechiae and noticeable pallor. No drug with which blood dyscrasia could be associated had been given at any stage of the child's illness.

The infant was admitted to hospital on June 11, 1955, aged 6 weeks and weighing 7 lb. 7 oz. (3,370 g.). Nutrition and hydration were good. The child was alert and afebrile, but there was marked pallor with petechiae in the mouth and skin. The liver was palpable and enlarged. The spleen could be felt $\frac{1}{2}$ in. (2 cm.) below the costal margin. No lymphadenopathy was apparent. No other abnormality was found on physical examination. The urine was normal.

Investigations on Admission.—Hb. 5 g. per 100 ml.; white cells, 63,000 per c.mm., with a preponderance of granular cells and a marked shift to the left (for differential count, see Table I). The red cells showed frequent polychromatic forms and normoblasts. Blood group B, rhesus test positive (to anti-D), direct Coombs test negative. Platelet count

FIG. 1.—“Platelet transfusions” are indicated by arrows, and transfusions of stored blood by dotted arrows. The duration of a normal bleeding-time is shown by a continuous black line; where this is interrupted the bleeding-time was found to be longer than 10 minutes.

(Fonio's method), 3,600 per c.mm. Bleeding-time in excess of one hour. Clotting-time, clot retraction, and prothrombin times were within normal limits. Hess's test showed 15 petechiae in $\frac{1}{4}$ square inch (3.2 square cm.). Serum bilirubin, 0.4 mg. per 100 ml. Tibial marrow counts (Table I) showed a normoblastic hyperplasia, active leucopoiesis, and a striking absence of platelet precursors. Prolonged search of several films from each specimen failed to show any mature or early forms of megakaryocytes. A maternal blood count was normal, with a normal platelet count. The Wassermann reaction in the mother and child was negative.

After admission a tentative diagnosis of congenital hypoplastic thrombocytopenia was made, based on the absence of platelet precursors, the haematological condition being associated with skeletal abnormalities.

On June 14 a transfusion of stored blood was given. In spite of a satisfactory rise in haemoglobin there was no appreciable effect on the bleeding-time or the platelet count, and the stools continued to be heavily blood-stained. In view of the thrombocytopenia, platelet transfusions were given (for technique, see Appendix). The improvement on each occasion was striking but transitory (Table II). Clinically, there was fading of petechiae, and the stools changed from melaenic to normal. The increased number of circulating platelets persisted for as long as five days, while the bleeding-time and the capillary fragility were found to be normal for a longer period (see Fig. 1).

TABLE I.—Blood and Bone-marrow Findings

	Blast Cells	Premye- loctes	Neutro- phil Mye- loctes	Neutro- phil Metamy- loctes	Segmented Neutro- phils	Lympho- cytes	Mono- cytes	Plasma Cells	Proery- throblasts	Early Normo- blasts	Inter- mediate Normo- blasts	Late Normo- blasts	Megakaryo- cytes
Marrow Counts (%)													
14/6/55	6.0	3.5	13.0	10.5	24.5	8.0	—	—	1.5	13.0	14.0	6.0	None seen
1/7/55	5.2	6.8	16.0	14.0	28.0	18.4	3.2	—	0.4	2.0	2.8	3.2	" "
23/9/55	3.6	4.4	15.8	15.4	24.0	24.8	—	—	0.4	1.6	7.6	2.4	" "
2/12/55	4.4	3.2	15.2	9.6	21.2	18.8	1.6	0.4	0.4	1.2	10.8	13.2	" "
Pre-transfusion Blood Counts (%)									Normoblasts per 100 W.B.C.			Total W.B.C.	
13/6/55	2.5	5.0	30.0	7.0	34.5	14.0	6.5	0.5	9			63,800	
2/8/55	—	—	5.0	4.0	43.0	33.0	15.0	—	(Reticulocytes 5.6%)			20,100	
10/10/55	—	—	2.5	0.5	53.5	39.0	4.5	—				18,800	
1/11/55	—	—	1.0	—	64.0	30.0	5.0	—				19,800	
9/11/55	2.0	1.0	1.0	7.0	48.0	34.0	6.0	1.0	28			131,000	
1/12/55	—	—	—	1.0	50.0	44.0	5.0	—	12			36,300	

TABLE II

Date	Volume of Blood	Platelet Content (per c.mm.)	Expected Rise (per c.mm.)	Actual Rise (per c.mm.)	Duration of Normal Bleeding- time
14/6/55	150 ml. (stored)	Nil	Nil	Nil	Nil
23/6/55	110 " (fresh)	—	—	3,300	5 days
29/6/55	250 " "	100,000	75,000	21,000	3 "
7/7/55	270 " "	195,000	146,000	65,000	4 "
6/8/55	200 " (stored)	Nil	Nil	Nil	Nil
11/8/55	220 " (fresh)	490,000	270,000	206,000	4 days
9/9/55	350 " "	536,000	430,000	150,000	12+ "
24/9/55	350 " "	113,000	84,000	12,000	4 "
13/10/55	350 " "	156,000	107,000	12,000	4 "
26/10/55	400 " "	668,000	486,000	104,000	8+ "
24/11/55	270 " (stored)	220,000	—	—	Nil

In addition to treatment with transfusion, cortisone was given by mouth. Therapy was begun with a dosage of 7.5 mg. daily, which was gradually increased to an ultimate dose of 24 mg. daily. Some control of the bleeding tendency appeared to be produced, as shown by improvement in tests of the bleeding-time and capillary fragility. There was no effect on the platelet count. In spite of anaemia the general condition of the child remained good, with satisfactory developmental progress (see Fig. 2, taken on October 11), and a slow weight gain from 7 lb. 7 oz. (3,370 g.) on admission to 14 lb. 3 oz. (6,435 g.) at death six months later.

After a poor response to two platelet transfusions, splenectomy was carried out on October 26. At operation the spleen was found to be slightly enlarged (weight 21 g.). Microscopy showed abundant splenic follicles with a simple pulp hyperplasia. There was no evidence of leukaemia, vascular lesions, or other abnormality apart from mild siderosis. As a pre-operative measure a particularly large platelet transfusion was given. There was no undue bleeding at the time of operation or during the post-operative period ;

wound healing was satisfactory, only superficial petechiae occurring at the operation site. Transfused platelets survived for three days. Nineteen days later, however, platelets appeared spontaneously, in small numbers, for the first time, preceded by the appearance of large numbers of normoblasts (28 per 100 white cells), together with reticulocytes (16.8%), and followed by a rapid rise in haemoglobin. The

FIG. 2.—Showing the deformity of the forearms and degree of enlargement of the liver.

improvement was not maintained. Four days after an emergency transfusion of stored blood the haemorrhagic state became more marked ; the infant developed signs of cerebral haemorrhage and died on December 2.

At necropsy an extensive cerebral haemorrhage was found. Absence of the radii was confirmed by dissection, no bony rudiment being demonstrable. Microscopy of the liver (weight 240 g.) showed small foci of haemopoietic tissue within the sinusoids. The lymph nodes generally were moderately enlarged, and microscopically showed similar haemopoiesis within the sinuses. A sample of bone marrow taken three hours after death showed a hypercellular, actively normoblastic marrow. Megakaryocytes were not seen in these films, nor in subsequent bone-marrow sections. Small haemorrhages were present in the lungs, myocardium, meninges, and brain. The haemopoietic activity was considered to be in keeping with compensatory blood formation following continued bleeding.

Diagnosis

Thrombocytopenia in the neonate is an uncommon condition. A comprehensive review of such cases is given by Robson and Walker (1951). They classify congenital and neonatal thrombocytopenia into those cases in which there is a maternal history of purpura and those from normal mothers. In the latter category they distinguish transient idiopathic thrombocytopenic purpura, in which hyperplasia of the megakaryocytes is the usual finding, from other cases in which there is an aplasia of the megakaryocytes in the bone marrow. The earliest reference to this latter condition is that of Greenwald and Sherman (1929). Two further cases have been recorded (Landolt, 1948 ; Stefanini and Dameshek, 1955). In each of these cases the child had one or more congenital deformities associated with hypoplasia of the megakaryocytes. The case of Stefanini and Dameshek appears remarkably similar to our own, since the hypoplasia of the megakaryocytes was associated with a congenital absence of both radii.

It is significant in this case that the mother's blood picture was normal, and that she gave no history suggestive of a haemorrhagic diathesis. There was a history of threatened abortion at the second month. It is at about this time in intrauterine life that platelet production is thought to begin (Fruhling *et al.*, 1949). In addition, there was no evidence of secondary thrombocytopenia in the infant arising from such causes as acute infection, drugs, or leukaemia. The fall of haemoglobin associated with the presence of normoblasts in the peripheral blood raised the possibility of a haemolytic anaemia, which was excluded by the absence of jaundice, normal serum bilirubin, and the negative Coombs test. Aplastic anaemia associated with skeletal defects of the type described by Fanconi (1927) could be excluded by the bone-marrow findings, the high white cell count, and the absence of other features such as cutaneous pigmentation and microcephaly. It is suggested that this is a case of primary congenital aplasia of the megakaryocytes associated with other congenital deformities, as referred to by Hauser (1948).

Platelet Transfusion

Platelet transfusions may be given by a variety of techniques, all based on preventing platelets adhering to wettable surfaces. Duke (1910) reported the first successful platelet transfusion, but gave no details of his technique. Hirsch *et al.* (1950) succeeded in raising the platelet count of a case by using silicone-coated syringes and needles. Recently, with the development of plastic materials, it has been possible to use non-wettable tubing for continuous transfusion rather than the multiple-syringe technique used by Hirsch and Gardner (1952) and Stefanini and Dameshek (1953). The latter authors reviewed other methods of obtaining platelet suspensions. These included the use of dextran, the collection of platelets on columns of ion-exchange resin, or the centrifuging of blood at low temperatures to remove red and white cells. They concluded that the manipulations necessary for these methods so impaired the survival of platelets after transfusion that they defeated their own purpose. The method adopted here is both simple and convenient (see Appendix).

We confirm the striking decrease in haemorrhagic manifestations, bleeding-time, and capillary fragility which has been reported by other workers, notably Duke, Hirsch, and Dameshek. Besides the use of platelet transfusions in the present case, stored blood and cortisone were given (see Fig. 1). Stored blood did not have any appreciable effect on the haemorrhagic state or on the maintenance of haemoglobin. This is illustrated by the transfusion given initially and that given on August 6. After the latter transfusion the haemorrhagic diathesis became so marked, with generalized petechiae, bleeding gums, and the passage of bright red blood in the stools, that the haemoglobin fell from 18.5 to 8.5 g. per 100 ml. in three days. This state was arrested by a transfusion of fresh blood containing 490,000 platelets per c.mm., with an improvement of the capillary fragility to normal, and a reduction of the bleeding-time to within normal limits. These effects lasted for four days, after which no platelets could be found in the infant's blood. Eight such "platelet transfusions" were given, including three from a donor with a platelet count of approximately 1,000,000 per c.mm., followed by a similar improvement on each occasion. It can be seen from Fig. 1 that, irrespective of the number of platelets present in the infant's blood immediately following transfusion, the survival of significant numbers of transfused platelets in the circulation remained the same (from four to five days).

Some platelets presumably disappear during the first few hours, being used to control capillary haemorrhage. It is interesting to speculate on the mechanism for the removal of the remainder, since it has been observed by us, and by Mustard (1956), that platelets can be stored in acid citrate-dextrose mixtures at 4° C. for periods of at least three weeks. Tullis (1953) has shown that platelets can be stored in special media for longer periods than either red or white cells.

Blood containing 220,000 platelets per c.mm. at the time of transfusion, in which the platelets had a normal morphological appearance and staining properties in spite of storage in a siliconed container for four weeks, was used on November 24. No platelets were demonstrable in blood samples taken from the infant immediately after this transfusion. We conclude that platelets whose staining and morphological appearance are normal are not necessarily viable. For the administration of viable platelets, freshly taken blood is essential.

On each occasion that platelets were transfused, an estimate of the expected rise was made, based on the platelets present in the blood passing through the needle to the infant and the assessment of the infant's blood volume derived from its weight—reckoning a blood volume of 40 ml. per lb. (Russell, 1949). It was noticed that in the later transfusions the difference between the actual platelet count performed on the infant and the expected level was becoming greater. From Table II it can be seen that in the initial platelet transfusions yields of between 30 and 70% were

obtained. These figures are similar to those recorded by Hirsch and Gardner (1952). These yields fell to a level of only 10% prior to splenectomy. Following the transfusion on October 13 the platelet survival time became shortened, and subsequent studies revealed the presence of a platelet antibody. Serum taken on October 20 showed a titre of 1/16 with compatible platelets, and a sample taken terminally on December 2 showed a titre of 1/8, using the technique described by Stefanini *et al.* (1953).

The low titre of antibody in this case and its failure to rise in spite of repeated platelet transfusion might be accounted for by the immaturity of antibody-producing mechanisms in the neonatal period. Cortisone possibly also impaired antibody production. Unfortunately, antibody was not looked for in the serum on admission, but the clinical course and the persistence of thrombocytopenia and antibody make transplacental transfer of antibody from the mother extremely unlikely in this case.

Splenectomy was undertaken as a last resort, since after two months' treatment, including cortisone, there had been no sign of autogenous platelet production, and the frequency of transfusions was increasing. We were influenced also by the case reported by Stefanini and Dameshek (1955), in which splenectomy was followed by a rise in the platelet count to normal numbers. In the present case, although platelets returned in small numbers a fortnight after splenectomy, the improvement was only transitory.

Hirsch and Gardner (1952), in discussing the largest series of platelet transfusions recorded, pointed out that, of 42 transfusions given, only one failed to produce clinical improvement, and in this case there was no rise in platelets. We agree that haemorrhagic manifestations in states of thrombocytopenia can be dramatically arrested, but this effect is only transient, depending apparently upon the survival of the platelets. This method of treatment has the limitation that if repeated, especially in adults, sooner or later the platelet survival time becomes shorter owing to the production of a platelet antibody. We suggest that it is well worth while to administer fresh blood from siliconed containers through plastic tubing to cases with thrombocytopenia, in order to tide them over acute haemorrhagic episodes or operative procedures such as splenectomy.

Summary

A case of congenital hypoplastic thrombocytopenia associated with other congenital defects is described with post-mortem findings.

Similar cases are briefly reviewed and the differential diagnosis is considered.

The progress and treatment with platelet transfusions, cortisone, and splenectomy are described and discussed.

Repeated platelet transfusions have been found to be of value and a simple technique is outlined.

Information regarding the survival of platelets *in vivo* and *in vitro* following transfusion has been obtained.

The value and limitations of platelet transfusion are discussed.

APPENDIX: METHOD USED FOR PRESERVING PLATELETS

Blood for transfusion was taken from fasting donors with a wide-bore needle direct into a known volume of acid-citrate-dextrose solution in a siliconed glass bottle calibrated in cubic centimetres. The bottles were prepared by coating the inside with silicone fluid D.C. 550 diluted with ether 1 in 2. The bottles were rinsed with several changes of glass-distilled water, dried in the incubator, and sterilized by autoclaving at a pressure of 20 lb. per square inch (1.4 kg. per square cm.) for 30 minutes. The blood on each occasion was then administered within one hour by scalp-vein transfusion through a short length—about 2 feet (60 cm.)—of "polythene" tubing. Transfusions were given rapidly at the rate of 40–50 ml. an hour. By these methods it was anticipated that the loss of platelets in the transfer of blood from donor to recipient would be reduced to a minimum.

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PULMONARY OEDEMA DUE TO ANGIOCARDIOGRAPHY

TREATMENT WITH INTRAVENOUS HYDROCORTISONE

BY

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Serious reactions to contrast media containing iodine are a not uncommon sequel to angiocardiology. Dotter and Jackson (1950) reported 26 deaths out of a total of 6,824 investigations, an incidence of 0.38%. Respiratory difficulty, respiratory arrest, or pulmonary oedema occurred in 12 of the fatal cases. McAfee (1955) reported eight deaths in a series of 732 angiocardiology. He found that patients with primary pulmonary hypertension and pulmonary stenosis appeared to be especially liable to develop serious reaction. Two deaths were reported following selective angiocardiology: in one patient, with multiple pulmonary arteriovenous aneurysms, 35 ml. of a 70% solution of diodone was injected through a catheter in the right atrium; the patient died from acute pulmonary oedema after twenty-five minutes.

We report below the case-history of a patient who developed fulminating pulmonary oedema after the injection of sodium acetrizoate into the pulmonary arteries.

Case Report

A man aged 39 had been well until a brief attack of unconsciousness during a strenuous game of football thirteen years previously. After this episode he became slightly breathless on exertion. He had a further syncopal attack, again precipitated by exertion, seven years ago. After a herniorrhaphy in January, 1955, he developed pulmonary infarction. There had been no other history of chest illness. He was admitted for investigation in November, 1955. On examination there were signs of pulmonary hypertension: a dominant "a" wave in the jugular pulse, an early ejection sound at the pulmonary area, and an accentuated pulmonary component of the second heart sound. The electrocardiogram showed right bundle-branch block. The chest x-ray picture showed moderate dilatation of the main branches of the pulmonary artery, with narrowing of the peripheral vessels.

The differential diagnosis included primary pulmonary hypertension, chronic thrombo-embolic pulmonary hypertension, and Eisenmenger's syndrome. Cardiac catheterization confirmed the presence of pulmonary hypertension. The pulmonary artery pressure was 90/20 mm. Hg, and the pulmonary vascular resistance was 10 units. The brachial arterial oxygen saturation was 91%. There was no direct or reversed shunt at any level. Selective angiocardiology was then performed to see whether any large pulmonary vessels were occluded. Promethazine hydrochloride, 25 mg., had been given one hour previously. A test dose of 1 ml. of sodium acetrizoate was injected through the catheter into the pulmonary artery. As there was no reaction, 15 ml. was injected into the left pulmonary artery, and a film taken. Then 20 ml. was injected into the right pulmonary artery and a further film taken.

At 11.15 a.m., forty-five minutes after the injection, the patient complained of nausea, and became dyspnoeic and slightly cyanosed. He also coughed up small amounts of frothy blood-stained sputum. He was given 50 mg. of diphenhydramine hydrochloride by mouth, but his condition became steadily worse. By 12.30 p.m. he was very distressed and breathless, and fine crepitations due to acute pulmonary oedema were widespread. He was transferred to a "cardiac" bed, venous cuffs were applied to the thighs, and he was treated with morphine, adrenaline, aminophylline, and oxygen without benefit. At 2 p.m. 25 mg. of promethazine hydrochloride and 200 mg. of cortisone were given intramuscularly. Oxygen was bubbled through 45% ethyl alcohol in a fruitless attempt to reduce the frothiness of the sputum. His condition progressively deteriorated, and he developed signs of extreme peripheral vasoconstriction, with an unrecordable blood pressure. He became increasingly drowsy, and by 4 p.m. he was unrousable; his upper respiratory tract was choked with profuse frothy sputum which he was unable to expectorate. Death appeared to be imminent.

At this stage, laryngoscopy was performed by direct vision and a considerable amount of sputum aspirated; this brought slight improvement. An intravenous injection of 5 ml. of nikethamide caused the patient to recover consciousness and expectorate a large amount of frothy sputum. He then gradually relapsed into coma. Thirty minutes later, at 4.45 p.m., a further dose of nikethamide produced a similar result. Then from 5 to 6.30 p.m. he was given an intravenous infusion of 100 mg. of hydrocortisone (free alcohol) in 500 ml. of isotonic saline. During this time his condition steadily improved, his breathing became less distressed, and he recovered consciousness. There were fewer rales in his chest. When 5 ml. of nikethamide was given intravenously at 5.45 p.m. he produced much less sputum than after the previous doses. At 6.30 p.m. the hydrocortisone was stopped, and a slow drip infusion was continued with isotonic saline alone; 25 mg. of promethazine hydrochloride was given intramuscularly. At 10 p.m. pulmonary oedema recurred and responded again to an infusion of hydrocortisone, which was continued until 1.30 a.m. At 3 a.m. a second relapse occurred, and the signs of pulmonary oedema diminished within five minutes of starting the third hydrocortisone infusion. This was maintained for three hours, and thereafter his condition remained satisfactory.

Oral cortisone was subsequently given in gradually decreasing doses for nine days. During this time he was pyrexial, and developed signs of consolidation of the apical segment of the right lower lobe; this was confirmed by radiography, and attributed to pulmonary infarction.

Discussion

Of the 26 deaths reported by Dotter and Jackson (1950), sensitivity tests were performed in 19 cases and were negative. Yet the intravenous injection of 1 ml. of solution of diodone has itself caused death in four instances (Morgan, 1950; McAfee, 1955). In the present case, generalized pulmonary oedema must be attributed to a hypersensitivity reaction of