birth. The severe jaundice appears, for want of evidence to the contrary, to have been of the "physiological" type, which is widely held to be a result of inadequate liver function. The presence of neonatal hepatitis was ruled out histologically and no significant infection was found anywhere.

Whatever the factors that led to kernicterus in the present case, it seems that a great deal of evidence now exists for the occurrence of symptomatic kernicterus as distinguished from a similar condition arising in conjunction with blood-group incompatibility. Thus a tentative aetiological classification of kernicterus may be put forward as (1) blood-group incompatibility; (2) a mixed group, comprising principally prematurity, and also severe infection, congenital anomalies, and maternal diabetes; and (3) cerebral damage following birth trauma.

Summary

A case of kernicterus is described in a full-term first-born infant in whom blood-group incompatibility was absent. The possible aetiology of the lesions is discussed, with particular reference to a coexistent intracranial haemorrhage.

Our thanks are due to Dr. B. E. Schlesinger and Dr. R. E. Bonham Carter, under whose care the baby was treated, and to Professor G. R. Cameron, for their advice. We are also grateful to Dr. Plaut, of the North London Blood Transfusion Service, for carrying out the serological testing.

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A STUDY ON THE A FACTOR AS A CAUSE OF HAEMOLYTIC DISEASE IN PREMATURE BABIES

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The view that anti-A and anti-B, as well as anti-Rh, can cause haemolytic disease of the newborn has been the subject of much controversy. The most common arguments against this view are based on the presumption that the abnormally increased titre of anti-A or anti-B antibody is the result of non-specific stimulation rather than a true iso-immunization such as occurs in the Rh system. Wiener (1951) thought that all the alpha and beta antibodies were of heterogenetic origin.

In recent years such arguments have lost some of their force because of accumulating evidence that there exist at least two varieties of A and B antibodies—namely, the complete (bivalent) and incomplete (blocking, immune, or univalent) ones. The behaviour of incomplete A and B antibodies is comparable to that of Rh

blocking antibodies (Boorman and Dodd, 1946; Polayes and McNally, 1948; Witebsky, 1948, 1949; Hubinont, 1949; Wiener *et al.*, 1949).

This report is designed to furnish additional evidence of sensitization to the A factor as a cause of foetal erythroblastosis resulting in premature birth and neonatal death.

Materials and Methods

Cord blood from the affected babies was examined for the A, B, M, N, C, D, E, c, and e antigens; red- and white-cell counts, and differential and haemoglobin estimations were also performed. The serum was titrated for the A, B, and Rh antibodies, and the icterus index was determined. Gross post-mortem examinations were also made on the infants, followed by histological studies.

The blood of the parents was examined for the same blood-group antigens; the mother's serum was tested for anti-A, B, Rh, Kell, S, Le^a, and Fy^a agglutinins, and, in addition, titrations were carried out upon it for complete and incomplete A and B antibodies.

Four methods were employed to detect and titrate the antibodies: (1) the conglutination method of Wiener *et al.* (1947), (2) the trypsinized red-cell method (Morton and Pickles, 1947), (3) the anti-human-globulin test of Coombs *et al.* (1945), and (4) the neutralized serum method of Witebsky and Engasser (1949). Methods 2 and 3 were modified so that they could be applied to the ABO system.

Case 1

A white woman aged 19, a primigravida, was admitted to the department of obstetrics and gynaecology, Quincy City Hospital, because of irregular labour pains in about the 33rd week of gestation. Menstruation had begun at the age of 11, the cycle being 26 to 30 days, with periods lasting from four to six days. She was married in September, 1949, and strongly denied abortion prior to this pregnancy. To the best of her knowledge she had never felt menstrual moulins except at the onset of the present gestation, and had never received any injection of or had been transfused with whole blood or with blood products. In childhood she had been vaccinated against whooping-cough and diphtheria.

Physical examination showed a pregnant woman weighing 179 lb. (81.2 kg.), without oedema, anaemia, or jaundice. Temperature, respiration, and pulse were within normal limits. Her blood pressure was 130/78, 120/80, and 120/80 mm. Hg on three consecutive days. A serological test for syphilis (Hinton) gave a negative result. The erythrocyte count was 4,800,000 per c.mm., haemoglobin 14.2 g.% and white blood cells 8,500 per c.mm.; the differential count was non-contributory.

Spontaneous delivery took place under anaesthesia and was uneventful. Five days after parturition the fasting blood sugar was estimated at 110 mg. per 100 ml. of blood. Urinary examination for casts, albumin, blood, and sugar gave negative results.

The baby, a boy, was born on June 13, 1950, and weighed 4 lb. 4 oz. (1,920 g.); he had no deformity. The umbilical cord and sclerae were reported to be moderately icteric. Cutaneous petechial haemorrhages were observed at the extremities. The heart sounds were normal, but there were diminished breath sounds in the left chest. The liver and spleen were not palpable. He was kept in an incubator at 90° F. (32.2° C.), the treatment consisting of injections of "crysticillin," 30 ml. of whole compatible blood, calcium gluconate, vitamin K, and nikethamide. He died after three days and seven hours.

His red-cell count was 3,800,000 per c.mm., haemoglobin 13 g.%, and white-cell count 18,000 per c.mm.; the differential count gave 1% promyelocytes, 2% myelocytes, 4% band forms, 37% segmented cells, 1% basophils, 9% eosinophils, 6% monocytes, and 40% lymphocytes. The stained

cord-blood smear showed 105 nucleated red cells (97 normoblasts and 8 erythroblasts) per 100 white cells. The icterus index was 56 units.

The necropsy confirmed the clinical findings of jaundice and petechial haemorrhages. A small amount of free blood was found in the pleural cavities. The upper lobe of the left lung was collapsed, while the others were normal. The liver and spleen weighed 80 and 8 g. respectively, being slightly enlarged. The heart appeared normal. Kernicterus was not observed in the brain substance. Microscopically, the liver, spleen, and kidneys showed excessive extramedullary haemopoiesis. The results of serological examinations of the family are shown in Tables I and II.

TABLE I.—Case 1. Blood Groups of Family

Subject	Blood Groups	Remarks
Mother ..	O M CDe/cde Secretor	Anti-N, S, K, Le ^a , and Fy ^a ; negative
Father ..	A ₁ N CDe/cde	"
Baby ..	A ₁ MN CDe/cde	Born in June, 1950, male; premature; died

TABLE II.—Case 1. Titration of Mother's and Baby's Sera

Medium	Antigen						Remarks
	A ₁ cde/cde		A ₂ cde/cde		B cde/cde		
	Mother	Baby	Mother	Baby	Mother	Baby	
Saline ..	6,100*	—	1,000	—	600	—	Method 3, phase I
Plasma ..	41,000	—	3,100	—	1,300	—	Method 1
Trypsinized cells ..	66,000	—	4,100	—	2,000	—	" 2
Coombs's serum ..	98,000	—	5,100	—	3,100	—	" 3, phase II
Neutralized serum ..	5,100	4,100	0	0	0	0	Method 4

* This is a twofold dilution starting from 1:2 or 1:3 or 1:10. The reciprocal value of the highest serum dilution which gives a definite positive reaction is taken as the final titre. For simplification, in cases where the titre exceeds 500 it is recorded in round figures—e.g., 6,100 and 98,000 instead of 6,144 and 98,304, etc.

— = not tested. 0 = no agglutination.

Case 2

A white woman aged 26, a 3-gravida, was admitted shortly after delivery, at home, of her third child. Menstruation, regular, 30 days cycle, and lasting five to six days, started at the age of 13. The first two pregnancies were uneventful, and resulted in 1946 and 1948 in the birth of full-term babies weighing 7 lb. 14 oz. (3.6 kg.) and 6 lb. 11 oz. (3 kg.) respectively. Physical examination showed her to be a well-developed and well-nourished woman, without oedema, anaemia, or jaundice, and the body temperature, respiration, and pulse were within normal ranges. The blood pressure was 110/70 mm. Hg, and the serological test for syphilis (Hinton) was negative. Urine examination showed a trace of albumin without any casts. Three days after delivery the fasting blood sugar was 118 mg. per 100 ml. of blood.

The baby—a female—was born on July 8, 1950, without apparent congenital malformation, and weighed 2 lb. 13 oz. (1,280 g.). She looked moderately icteric and her general condition was poor. No haemorrhage or discharge of blood was noticed. The baby received the same treatment as in Case 1, but died within 10 hours of admission.

Her erythrocytes numbered 3,600,000 per c.mm., haemoglobin 13.4 g.%, white-cell count 19,500 per c.mm.; the differential count gave 1% promyelocytes, 1% myelocytes, 3% metamyelocytes, 4% band forms, 34% segmented cells, 1% basophils, 8% eosinophils, 5% monocytes, and 43% lymphocytes. A cord-blood smear showed 152 nucleated red cells (140 normoblasts and 12 erythroblasts) per 100 white cells. The icterus index was 46 units.

The necropsy failed to reveal evidence of bleeding but confirmed the jaundice. The upper lobe of the right lung

was atelectatic, while the other lobes were generally normal. The liver and spleen were slightly enlarged and weighed 68 and 6 g. respectively. The heart did not show any significant pathological change. The brain weighed 280 g. and did not show kernicterus. On microscopical examination extensive extramedullary haemopoiesis was observed in the liver and spleen. Erythropoiesis continued to be markedly extravascular, apart from the clusters of nucleated red cells in the liver sinusoids.

The serological investigations are shown in Tables III and IV. The fact that the father and baby belonged to the intermediate group A₁-A₂ was ascertained by the difference in quantitative titration, shown in Table V.

TABLE III.—Case 2. Blood Groups of Family

Subject	Blood Groups	Remarks
Mother ..	O MN CDe/cde Secretor	Anti-E, S, K, Le ^a , Fy ^a ; negative
Father ..	A* M CDe/cde†	"
First baby ..	O MN CDe/cde	"
Second baby ..	‡	Male, born in 1946; living and well
Third baby ..	A* M cde/cde	Female, born in 1948; living and well
		Male, born in July, 1950, premature; died

* Intermediate A₁-A₂ type (see Table V).

† The father's genotype cannot be CDe/cde because his wife and two of the children have genes "cde" and one of them is of genotype cde/cde.

‡ Unable to come for investigation.

? = Unidentified.

TABLE IV.—Case 2. Titration of Mother's and Third Baby's Sera

Medium	Antigen						Remarks
	A ₁ cde/cde		A ₂ cde/cde		B cde/cde		
	Mother	Baby	Mother	Baby	Mother	Baby	
Saline ..	1,500	—	160	—	128	—	Method 3, phase I
Plasma ..	2,600	—	320	—	256	—	Method 1
Trypsinized cells ..	4,100	—	500	—	320	—	„ 2
Coombs's serum ..	6,100	—	1,000	—	500	—	„ 3, phase II
Neutralized serum ..	1,000	770	0	0	0	0	Method 4

TABLE V.—Quantitative Titration of Immune A antibodies with Red Cells of Intermediate A₁-A₂ Type

Titre of Immune A Antibodies*	Red Cells of Father (Case 2)	Red Cells of Third Baby (Case 2)	Control A ₁ Cells	Control A ₂ Cells
1:32 ..	+++	+++	+++++	0
1:64 ..	+++	++	+++++	0
1:128 ..	++	+	+++++	0
1:256 ..	++	+	+++	0
1:512 ..	+	±	+++	0
1:1,024 ..	+	0	++	0
1:2,048 ..	±	0	++	0
1:4,096 ..	0	0	+	0
1:8,192 ..	0	0	+	0

* One part of immune A serum is first neutralized with two parts of A-B substances. Dilutions were made in normal AB serum (undiluted).

0 = no agglutination. ± = weak agglutination. + = definite agglutination. ++ = strong agglutination. +++ = very strong agglutination. ++++ = extremely strong agglutination.

In addition, the sera from the two mothers were tested against a panel of O cells having the specificity for S(MN), Kell, Lewis, and Duffy antigens, all with negative results.

Discussion

Iso-immunization to the A₁ factor in a first pregnancy (Case 1) and to the A₁-A₂ factor (Case 2), resulting in premature birth and foetal erythroblastosis, is seldom recorded in the literature. That iso-immunization to the A-B factors with fatal consequences is not more frequently brought to light may be due to the following reasons: (1) The A-B factors are not generally accepted as a cause of severe foetal erythroblastosis. (2) More attention has in the last decade been focused on Rh incompatibility as a cause of foetal death. (3) Many

premature babies die very soon, so that serological and systematic investigations are not possible. Without such study, death in these cases is often recorded as due to prematurity and atelectasis.

Mild cases of erythroblastosis caused by the A-B factors in first and subsequent heterospecific pregnancies have been reported by Halbrecht (1944), Wiener *et al.* (1949), and Brancato (1950). Halbrecht introduced the term "icterus praecox," which is now widely accepted. Recently he stated that icterus praecox occurred not less frequently than the other forms of haemolytic disease, the proportion being 1 in 25 to 1 in 30 of heterospecific pregnancies (Halbrecht, 1951).

The argument that the mother in Case 1 might have had a previous missed abortion, coinciding with the time of expected menstruation and thus escaping her notice, deserves comment. In such a case the foetus could be only a few weeks old, and its blood group agglutinogens would probably not have developed enough to sensitize the mother. Mackenzie (1950), moreover, considered menstrual molimina to be one of the earliest presumptive signs of gestation.

The baby in Case 1 is known to have been a secretor. The secretor status of Case 2, however, cannot be stated definitely, even though the parents are both secretors, since we were unable to obtain sufficient material for the inhibition test. It is still a controversial matter whether the maternal A and B antibodies affect secretor babies or not. Levine (1946) assumed that only non-secretor babies are affected by those antibodies. On the other hand, Wiener *et al.* (1949), having found that secretor babies were also afflicted with haemolytic disease, concluded that such antibodies did not act directly on the tissue cells, but apparently produced damage through the blood stream, presumably by agglutinating the red cells and thus blocking the circulation. We have observed only one case in which a secretor baby is affected, and we cannot therefore offer an opinion. Further intensive and careful investigations on a large number of similar cases are necessary before a definite conclusion can be warranted. The real problem is rather that of finding out why all babies with appropriate blood groups do not suffer from haemolytic disease.

Summary

Two serologically and histologically proved cases are reported of iso-immunization to the A factor, resulting in the birth and neonatal death of infants suffering from erythroblastosis. In the first case, sensitization to the A₁ factor occurred in the first pregnancy of a young woman, and in the second case to the intermediate A₁-A₂ type in a third pregnancy.

In Case 2, differentiation between A₁, intermediate A₁-A₂, and A₂ is required, and is shown by the quantitative method.

The significance of serological investigation of premature babies is discussed.

We wish to express our thanks to Drs. E. Nathan and I. Edelstein for kind permission to study their private patients, to Miss Eda Deitsch, M.T., Miss Kathryn Crane, and Miss Alexandra Codakes for technical assistance, and to Dr. A. E. Mourant for suggestions and criticism.

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A PECULIAR SYNDROME OF "BLADDER PARALYSIS" IN NATIVES OF SOUTH CENTRAL AFRICA

BY

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For some years in this hospital we have become increasingly aware of a form of bladder "palsy" in the male African adult with urinary bilharziasis, running as a rule a typical course of brief duration followed by complete recovery.

The patient is generally between the ages of 20 and 50, previously in good health, and first observes a fairly rapid inability to void urine. The difficulty increases over a day or more, less urine being evacuated with each effort. He next finds he cannot pass any at all, the bladder at this stage becoming grossly distended. All efforts to pass urine are without avail; but while he may have some pain, it is never severe or as discomfiting as is usual with other forms of retention. The next stage is one of dribbling or overflow incontinence, a few drops of urine issuing from the distended viscus. At this stage the patient generally seeks medical aid at the hospital, being admitted as a case of "acute retention." When seen the diagnosis usually made is one of obstruction due to a urethral stricture, an enlarged prostate, or perhaps a calculus. Yet a striking feature is the relative comfort and ease of the patient (Fig. 1) and the absence of anything to support an obstructive disturbance.

A small soft catheter can be passed without difficulty. Instead of encountering any form of obstruction or resistance, it will be found to pass with perfect ease into the bladder, which is then emptied. A little puzzled, one withdraws the catheter only to find that after some hours the bladder tumour appears again, the patient being totally unable to void, and so the catheter is again passed and the whole performance repeated. The patient is thus in a state which might best be described as *complete atony of the bladder*. He knows his bladder is full, but in spite of this he is not disturbed, and appears to be fairly comfortable. This stage lasts several days, and then the organ seems to regain its "tone" and a similar process in reverse to the onset denotes the stage of recovery. The bladder slowly appears to regain its former tone, the degree of retention becoming progressively less over a couple of days and the amount voided increasing.

The patient has now recovered, and as a rule recovery may be regarded as permanent. Occasionally, however, we have seen a relapse after a few weeks, the second attack being less severe and recovery more rapid; nevertheless, the same stages as already described are seen.

A Typical Case

An intelligent African male aged about 22 was admitted to the Salisbury Hospital on August 9, 1951, with acute retention with overflow of some two days' duration (Fig. 2).

FIG. 1.—A patient with well-marked distension of bladder.