FOETAL CELLS IN THE MATERNAL CIRCULATION DURING PREGNANCY

BY

W. WEINER, M.D.

Director, Regional Blood Transfusion Service, Birmingham

ROSALIE M. CHILD, M.B., Ch.B.

Department of Pathology, Manor Hospital, Walsall

J. M. GARVIE, B.M., M.R.C.P., D.C.H.

Consulting Paediatrician, Manor Hospital, Walsall

AND

W. H. PEEK, M.R.C.S., L.R.C.P., M.R.C.O.G.

Consulting Obstetrician and Gynaecologist, Manor Hospital, Walsall

Levine, Katzin, and Burnham's (1941) brilliant exposition of maternal iso-immunization during pregnancy as the cause of haemolytic disease of the newborn has been vindicated in thousands of cases. Direct proof that this iso-immunization was due to an antigenic stimulus from the foetus was produced by Chown's (1954) investigation, which demonstrated foetal cells in the maternal circulation. A further paper on this subject was published by Dunsford (1957), who also found foetal cells amongst the maternal cells. In both cases the foetal cells were discovered in a blood specimen obtained after the birth of the baby. Chown's patient developed, after the usual latent period, an anti-rhesus antibody, thus making the picture complete. Bromberg, Salzberger, and Abrahamov (1956) succeeded in demonstrating foetal haemoglobin in the maternal circulation during some pregnancies, and as this could be shown not to be a normal occurrence it was also very suggestive of a "leak" in the placenta.

Case Report

A married woman aged 32 had an abortion at three months in 1953 and expected her first baby in June, 1955. Her blood group was determined on two occasions during this pregnancy as group A, rhesus negative. The serum gave no evidence of the presence of any abnormal antibodies. The baby was stillborn, but no cause for this stillbirth was found.

The patient became pregnant again in 1957, but her dates were quite uncertain; she thought that her E.D.D. was approximately mid-February, 1958, but when she attended for her first antenatal investigation on January 5, 1958, this did not seem to correspond to the clinical findings. A blood specimen gave both unexpected and unusual findings. The specimen grouped both by cell and by serum grouping as group A. However, when the cells were investigated for their rhesus group, an anti-C plus anti-D and an anti-D testing serum produced some agglutination, which to the technician seemed to be a result conflicting with our previous findings. A full investigation was therefore carried out, and this showed that both anti-C and anti-D sera produced small agglutinates "in a sea of unagglutinated cells," the typical picture of a "mixed field." Anti-E gave a negative result and anti-c almost complete agglutination. (All sera used were saline agglutinating "genotype" sera.) This investigation was repeated twice on cells from the same specimen and identical results were obtained. At the same time an investigation of the serum gave definite evidence of the presence of a low-titred blocking anti-rhesus antibody of anti-D specificity.

The presence of D-positive cells together with an anti-rhesus antibody caused us to investigate the cells for "coating," and the direct Coombs test was in fact found to be

quite strongly positive, though again a "mixed field" was noted. The specimen which had given these results was a small specimen of clotted blood, and to prepare an eluate the clot was passed through an ordinary tea sieve. The cells thus obtained were thoroughly washed and an eluate was prepared from them by the method previously described (Weiner, 1957). The eluate had typical anti-D activity when tested by means of the indirect Coombs test.

The patient was immediately written for and a further specimen was obtained (approximately eight days after the specimen described above). This further specimen, however, showed no trace of any D-positive cells in spite of the exhibition of very strong antisera. All cells were found to be rhesus negative (cde/cde). Also an indirect Coombs test with very strong blocking anti-D gave a negative result. The titre of the anti-rhesus antibody in the serum had, however, increased considerably in the meantime.

A specimen from the husband was found to be group O, rhesus positive, phenotype CcDEe (most likely genotype CDe/cDE).

From the results obtained it was concluded that the agglutinated cells in the first specimen had been derived from the baby and that these cells had been coated by a preformed maternal antibody. From the results obtained one could even predict the genotype of the baby as CDe/cde, though it was not possible to say anything about the baby's ABO group.

It was thought inadvisable to allow the pregnancy to go to full term, and a caesarean section was performed on February 8, when clinically it was thought that she was not at term. The baby's blood group was found to be A (identical with the mother's group) and to have the predicted genotype CDe/cde. The direct Coombs test was very strongly positive. Bilirubin was 7.9 mg. per 100 ml., but the haemoglobin was found at the very low level of 5.1 g. per 100 ml. The baby, a girl, weighed 6 lb. 11 oz. (3.04 kg.). Her clinical condition was very poor from the moment of birth. She was pale, grey, and oedematous. She was kept in continuous oxygen, and nikethamide was injected into the umbilical vein. An exchange transfusion was started as soon as possible. Although the exchange was smooth, it was stopped after about 65 ml. of blood had been exchanged per pound (143 ml. per kg.) body weight, because of the extremely bad condition of the baby. It was intended to repeat the procedure if her condition should show even a slight improvement after this initial exchange. However, the condition deteriorated still further, and the baby died approximately 15 hours after birth.

At necropsy a small tentorial tear, together with a large cerebral haemorrhage around the cerebellum and the base of the brain, was found. There were no effusions, the lungs were atelectatic and showed petechial haemorrhages. The liver and spleen showed the typical changes of haemolytic disease of the newborn with very active extramedullary haematopoiesis.

Discussion

Previous authors have reported foetal cells in the maternal circulation after the birth of the baby. These cells might, of course, have entered the maternal circulation during delivery, and the finding of these cells in the maternal circulation was most suggestive but not absolute proof of the presence of foetal cells in the maternal circulation during the pregnancy. We could demonstrate these cells, however, during the pregnancy and even describe their genetic make-up.

The exact date when the mother developed the anti-rhesus antibody is not known, and it is, of course, possible that it had developed after the second pregnancy—that is, before this baby was conceived. The antigenic stimulus could have been provided by the stillborn baby in 1955, similar to the cases described previously (Weiner and Hallum, 1950). We did not attempt to estimate the amount of foetal blood which had been "transfused" into the mother, as we were aware of the simultaneous presence of the maternal antibody

against them, making a quantitative assessment quite unreliable. The baby must, however, have bled extensively, as the extremely low level of haemoglobin (5.1 g. per 100 ml.) is unlikely to have been produced by haemolysis only. It seems much more likely that this low level was the result of blood loss plus haemolysis. The production of anaemia in babies through blood loss into the maternal circulation had been suggested by Wiener (1948), and we think that this case is a further example, though no doubt haemolysis played some part in the production of the anaemia.

Summary

A case of foetal blood loss into the maternal circulation is described. The foetal cells were recognized during the pregnancy in the blood stream of an immunized mother.

The maternal serum contained an anti-rhesus antibody which coated the foetal cells in the maternal circulation and gave rise to a positive direct Coombs test. It was successfully eluted from the coated cells.

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ADDENDUM.—Since this paper was submitted a further article on transplacental bleeding from the foetus (Goodall *et al.*, 1958) has appeared.

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INTRAVENOUS PHENTOLAMINE FOR PHAECHROMOCYTOMA AND "ADRENALINE SHOCK"

BY

R. BARRATT TERRY, M.D., M.R.C.P.
*Senior Physician in Education, Division of Medical
 Education, Cook County Hospital; Associate in
 Medicine, Northwestern University Medical
 School, Chicago*

JOHN R. TOBIN, jun., M.S.(Med.), M.D.
*Senior Physician in Education, Division of Medical
 Education, Cook County Hospital; Assistant Professor of
 Medicine, Stritch School of Medicine, Loyola University,
 Chicago*

AND

RICHARD B. O'CONNOR, M.D.
*Resident Physician in Medicine, Cook County Hospital,
 Chicago*

The management of the usual patient with phaeochromocytoma is now well established, with a welcome improvement in mortality (Kvale *et al.*, 1957). The most significant factor in this success has probably been the use of oral or intramuscular phentolamine ("rogitine"*) to block the effects of circulating adrenaline and nor-adrenaline (Iseri *et al.*, 1951; Emlet *et al.*, 1951; Newton *et al.*, 1955).

We wish to focus attention on the management of the unusual patient with phaeochromocytoma in whom the

classic symptomatology of the disease is punctuated by wild unpredictable fluctuations of the systemic blood pressure with periods of alarming hypertension alternating with periods of profound shock. Such a patient has recently been under our observation, and in this instance the usual doses of phentolamine intramuscularly were found to be ineffective; however, a continuous intravenous phentolamine infusion produced dramatic improvement and, we believe, was life-saving. It enabled us effectively and leisurely to organize a programme of therapy for the operative and post-operative periods.

Case Record

The patient, an 18-year-old coloured girl, was first seen at the Cook County Hospital on January 8, 1957. She complained of nervousness, sweating, difficulty in breathing, severe lower abdominal pain, and vomiting of four hours' duration. For one year prior to admission she had had daily episodes of sweating and nervousness which began on arising and persisted until noon. Upon inspection she was seen to be orthopnoeic, grey, cold, and perspiring. The oral temperature was 101° F. (38.3° C.). The blood pressure was 80/0. The pulse was barely perceptible, with a rate of 140. The cardiac rhythm was regular. The left heart border was 3 cm. left of the mid-clavicular line in the fifth interspace. The heart tones were not unusual. Auscultation of the lungs disclosed fine and coarse moist rales throughout both lung fields. Upon palpation of the abdomen, a rounded mass, approximately 3 cm. in diameter, was detected in the left upper quadrant; it was in close proximity to the left kidney. The remainder of the physical examination showed nothing of importance.

Following palpation of the left upper quadrant of the abdomen, the patient began to tremble, her dyspnoea increased, and she sat bolt upright. She complained of a "nervousness," first in her abdomen and then "all over." This sensation was followed by increasing abdominal pain. The blood pressure was recorded as 230/17. The symptomatology suggested the presence of phaeochromocytoma complicated by acute left ventricular failure. Immediate therapy directed towards the relief of the left ventricular failure was successful. Additional therapeutic measures included sedation, complete bed rest, and elimination of all procedures which might augment tumour secretion. The patient's condition remained grave. Hypertensive-hypotensive swings in the systemic pressure continued, despite the administration of phentolamine intramuscularly in amounts of 5 mg. every four hours. For a period of 24 hours the blood pressure fluctuated between 290/140 and 80/0.

One of us (R. B. T.) suggested that phentolamine be given by continuous intravenous infusion. A solution of 30 mg. of phentolamine in a litre of 10% dextrose and water was infused intravenously at a rate of 20–80 drops a minute, depending upon the systemic blood pressure. The response was dramatic. The patient's sweating, pallor, coldness, and weakness disappeared, and within two hours she complained of hunger and was able to eat with obvious pleasure.

After surgical consultation, all agreed that the patient should be explored, but in view of her response to intravenous phentolamine there seemed to be no reason for hasty action. Two and a half days were allowed to elapse before the condition of the patient was considered to permit laparotomy. We were thus able to alert all personnel who were to be concerned with her care; and detailed check lists were prepared of all the procedures and medications necessary for proper management during and following surgery. During the 60 hours prior to surgery the patient received 250 mg. of phentolamine, and the blood pressure and pulse were recorded approximately every half-hour. Adjustments in the rate of flow of the infusion served to control all signs of tumour secretion. The patient had no symptoms, and there were no further hypertensive-hypotensive swings in the blood pressure (see Chart).

*Known as "rogitine" in the U.S.A.