on Oct. 31, and since then the blood chemistry has remained satisfactory (Table I). In March, 1948, she was symptom-free, had gained 30 lb. (13.6 kg.) in weight, and was able to walk unsupported.

Discussion

The post-operative tetany was due to an abrupt fall in serum calcium. Efforts to raise the latter by parathormone (total 1,260 units) were unsuccessful even with different batches of the extract. That it was physiologically active was certain, since its effect in producing a diuresis was well marked. It was felt that failure to absorb calcium might account for the lack of response to the hormone, but faecal analysis for calcium showed that this was not so. It was concluded that the fall in serum calcium and the resultant tetany were due not to too little parathyroid tissue but to the "hungry bones" (Cope, 1941). After operation the decalcified skeleton absorbs calcium and phosphorus from the plasma with so much avidity that hypocalcaemia and hypophosphataemia result. The biochemical findings support this theory, the blood calcium and phosphorus both falling immediately after operation. The rise in alkaline phosphatase which occurred is interpreted as being due to increased osteoblastic activity associated with this recalcification.

The severe and almost fatal tetany which followed the transfusion of blood was produced in a different way. The introduction of citrate (the anticoagulant) would on account of its avidity for calcium ions cause a further reduction in the ionized calcium without altering the total calcium. "Citrate tetany" has been produced experimentally, but its occurrence after transfusion must indeed be rare unless, as was the case here, the serum calcium is already depleted.

The rise in serum calcium which started three days after large doses of calciferol had been prescribed was due to the specific effect of the drug and not to a spontaneous recovery, since the calcium fell again when the dosage of calciferol was temporarily reduced (Fig. 1). During its administration, also, the serum phosphorus rose slowly, while the alkaline phosphatase fell with remarkable rapidity and was normal eight weeks after operation. The calciferol did not appear to have any inhibitory effect on deposition of calcium or phosphorus in bone, for during a five-weeks period 69.25 g. of calcium and 14.84 g. of phosphorus were retained.

Not every case of parathyroid adenoma will require massive calciferol therapy in the post-operative phase. It will definitely be indicated when there is well-marked bone disease and should be started immediately after removal of the adenoma. In addition, large doses of calcium must of course be given orally, and until the calciferol takes effect symptoms of tetany may be alleviated by intravenous calcium gluconate; parathormone should not be used.

I wish to thank Professor C. F. W. Illingworth for allowing me to investigate this patient and Professors J. Norman Davidson and J. W. McNee for advice in the preparation of the paper.

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The Ministry of Health has issued a pamphlet, "Nursing and Domestic Staff in Hospitals," intended as a guide to hospital management committees on the recruitment, training, and conditions of service of nurses. It includes an example of how to work a shift system in a ward of 34 beds with a staff of one sister, two staff nurses, seven students for day duty, and two nurses for night duty, as well as some observations on what the proper task of a nurse should be and how some of the ward duties at present performed by nurses could be undertaken by domestic orderlies. These include arranging flowers, answering telephones and running messages, preparing meal trays, and handling clothing and laundry. The pamphlet has been sent to boards of governors of teaching hospitals and hospital management committees.

AGGLUTININ ANTI-P IN PREGNANCY REPORT ON TWO CASES

BY

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The detection of an antibody in the serum during pregnancy has had much significance since Levine and his co-workers (1941) first propounded the theory (since amply confirmed) that haemolytic disease of the newborn is caused by the action on the foetal erythrocytes of immune antibodies formed in the mother's serum during pregnancy and passed through the placenta into the foetal circulation. The formation of these antibodies is stimulated by an antigen present in the foetal red cells but absent from the maternal red cells, the antigen having been inherited from the father. In a very large proportion of cases it has been demonstrated (Boorman *et al.*, 1942) that the rhesus complex has been involved, and in a few the ABO system (Aubert *et al.*, 1945).

There are not many references in the literature to immune or naturally occurring anti-P, and a leading article in the *British Medical Journal* of Oct. 20, 1945 (p. 535), refers to a case in which anti-P was associated with pregnancy. Wintrobe (1946) states: "In rare cases iso-immunization apparently occurs against the agglutinogens A and B, and possibly even M and P may cause immune bodies to be formed." Nigg (1930) has described two human sera which were later found to contain natural anti-P iso-agglutinins, whilst Wiener (1943) records having found only three or four such sera during a period of ten years. The latter serologist also found this iso-agglutinin in two post-transfusion sera he investigated; he states that "while the possibility exists that this factor could on rare occasions give rise to haemolytic transfusion reactions, to date no such reactions have been reported."

During the course of routine investigations carried out in this laboratory, which included testing the patient's serum at 37° C. against a series of Group O cells chosen not only for their rhesus type but also for their M, N, P, Kellecher, Lewis, and Lutheran types, the agglutinin anti-P was discovered in the sera of two pregnant women. In view of the extreme rarity of such an occurrence the history and the serological findings in these two cases are presented below.

Case 1

Mrs. X, a 2-gravida aged 36, in 1940 had a full-term clinically normal child weighing 6 lb. 12 oz. (3.06 kg.), and was again due for delivery on July 31, 1947. There was no history of transfusion or injection of blood. A blood sample was sent from the antenatal clinic for rhesus typing.

Serological Findings

March 7.—Mrs. X:—Group O Rh-positive. Her serum agglutinated some Group O cells weakly at 37° C., giving much stronger reactions at room temperature and at 4° C. At the latter temperature it appeared specific for P cells with a titre of 4. These reactions were compared with those of a proved anti-P serum and were found to be identical, suggesting that Mrs. X's serum contained anti-P. The serum gave a strong Diamond (Diamond and Abelson, 1945) slide reaction. A sample of serum was submitted to the Blood Group Reference Laboratory, Lister Institute, and confirmed as anti-P.

May 9.—Mrs. X:—Group O; genotype cDE/cde; M, N, p. The titre of the antibody against the same Group O P cell was 16 at room temperature and there was no evidence of enhancing when pooled serum from Group O p persons was used in place of saline. Mr. X:—Group A Rh-positive; genotype CDe/cDE; M, N, P. His cells were strongly agglutinated by his wife's serum at 4° C. and room temperature, and weakly at 37° C after absorption with A p cells.

June 20.—Mrs. X:—The titre of the antibody was now 4 with the standard O P cell. There was no evidence of an

incomplete anti-P after destroying the complete antibody by heating at 70° C. for ten minutes and using the Coombs test (Race *et al.*, 1946) for incomplete antibodies.

Aug. 12.—Mrs. X was delivered of a normal infant. *Baby X*:—Group A Rh-positive; M, N, P. Direct Coombs negative. The mother's serum after absorption with A p cells agglutinated the baby's cells strongly at 4° C. and room temperature and weakly at 37° C. *Mrs. X*:—The titre of the antibody was 8, and it could not be enhanced.

Aug. 22.—The child was clinically normal and the haematological reports were normal. On the tenth day of Mrs. X's puerperium the titre of the antibody was 32 at room temperature and was confirmed by the Blood Group Reference Laboratory as anti-P.

Case 2

Mrs. Y, a primipara aged 27, was expecting delivery on Sept. 6, 1947. There was no history of transfusion or injection of blood. A blood sample was sent from the antenatal clinic for rhesus typing.

Serological Findings

March 8.—Group O Rh-positive (D+) p. Her serum agglutinated some O cells weakly at 37° C., but gave much stronger reactions at room temperature and at 4° C. At the latter temperature it appeared specific for P cells with a titre of 4. These reactions were compared with a proved anti-P serum and Mrs. X's serum (previously described) and were found to be identical. From this it appeared that the antibody was anti-P; a sample of the serum submitted to the Blood Group Reference Laboratory was confirmed as anti-P.

April 21.—The titre of the antibody was 32 at 4° C. and room temperature with standard Group O cells and there was no evidence of its enhancement. The titre at 37° C. was 2. There was no evidence of an incomplete anti-P.

June 28.—Mrs. Y's cells were fully investigated: Group O Rh-positive; genotype CDe/cde; M, N, p. The titre of the antibody had not changed.

Aug. 2.—No change in the strength of the antibody.

Aug. 26.—Mrs. Y was delivered of a normal baby. *Baby Y*:—Group O, apparently Rh-negative; P. Direct Coombs negative. Its cells were agglutinated by the mother's serum at 4° C., room temperature, and 37° C. *Mrs. Y*:—No change in the strength of the antibody, nor could it be enhanced.

Sept. 5.—Mrs. Y:—No change in the strength of the antibody. *Baby Y*:—Haematological reports normal; no signs of haemolytic disease of the newborn.

Discussion

The finding of these antibodies in the sera of two pregnant women immediately raises the questions: Are these antibodies immune or naturally occurring? and, Can they give rise to haemolytic disease of the newborn? The following criteria were used in order to arrive at a decision: (a) Could the titre of the antibody be enhanced? (b) Was there evidence of an incomplete form of the antibody? (c) The direct Coombs test on the infants' red cells. (d) The clinical condition of the children.

In investigating the possibility of enhancing the antibody titre the technique used was that first described by Boorman and Dodd (1945). They found that immune sera could be enhanced when normal human sera were used as the diluent in place of saline, whereas naturally occurring agglutinins showed no enhancing. Boorman and Dodd applied their technique to 81 immune and 14 naturally occurring agglutinins and included in their series cold agglutinins but not anti-P. Their technique has been confirmed in this laboratory. Although there were fluctuations in the titre of the antibodies in the two cases described, there was no evidence of enhancing when pooled human serum from Group O p donors was used as the diluent.

In cases of Group O people whose anti-A has been stimulated as a result of immunization with A-group-specific substance it has been shown that their sera contain an

incomplete form of the alpha agglutinin (Boorman and Dodd, 1946). This could be detected by destroying the complete agglutinin with heat and the finding of the incomplete form by the Coombs reagent. In the two sera here reported the complete agglutinin was destroyed by heating at 70° C. for 10 minutes and there was no evidence of an incomplete form of anti-P in that P cells were not sensitized when tested with Coombs reagent.

The second use of the Coombs reagent is for the detection of *in vivo* sensitization by a maternal antibody of the red blood cells of infants with haemolytic disease. These sensitized cells are agglutinated by an anti-human-globulin serum, whereas the cells of normal infants are not agglutinated. In the two cases here described the red cells of the infants were tested as soon as possible after birth and there was no evidence of sensitization. Finally, the medical officers in charge of the cases reported that the infants showed no clinical signs of haemolytic disease and developed normally.

These investigations suggest that the anti-P agglutinins were of natural occurrence and may be compared to the naturally occurring agglutinins anti-A and anti-B, which have occasionally been responsible for haemolytic disease of the newborn. The protective factors in heterospecific blood group pregnancies were studied by Tovey (1945). His assessment of the main mechanisms operating individually or in combination to protect the foetus may apply to these cases—namely, lack of permeability of the human placenta to these agglutinins, neutralization of the incompatible antibody crossing the placental barrier by group-specific substances in the foetal plasma, lack of sensitivity of the foetal erythrocytes towards the incompatible agglutinins, and diminished activity of the agglutinins at body temperature.

It would appear from these two cases that naturally occurring anti-P, although of sufficient strength to be active at 37° C. (Kettel, 1930: the thermal amplitude is usually directly proportional to the titre of the cold agglutinin), is unlikely to be a causative agent in haemolytic disease of the newborn. Conclusive evidence may be derived from further studies.

Summary

Two cases of pregnant women in whose sera the agglutinin anti-P was found are reported.

Evidence suggesting that these antibodies were of natural occurrence is offered.

It is suggested that this naturally occurring antibody is not of pathological significance.

The serological investigations were carried out in the laboratory of the National Blood Transfusion Service, Sheffield, and my sincere thanks are offered to the late and present blood transfusion officers (Dr. E. F. Aubert and Lieutenant-Colonel R. H. Malone) for their discussions and for permission to publish this paper. To Drs. J. B. Cochran and R. G. Cooke, of Nottingham City and Derby City Hospitals, for their co-operation, and to Drs. A. E. Mourant and R. R. Race, of the Lister Institute, for their confirmation of the anti-P sera.

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