A New Human Blood Factor of Rare Incidence in the General Population. (18793)

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On studying the serum of an Rh positive mother, Mrs. R. M., para 4, gravida 4, who delivered an infant suffering from severe hemolytic disease, an antibody was observed which reacted with the blood of the father, the oldest sibling, and the affected infant, but not with the bloods of the remaining 2 siblings. The factor was present in the blood of the infant's paternal grandmother, but not in his grandfather, nor in the blood of his father's 2 siblings. Thus, the agglutinogen was demonstrated in the blood of 4 out of 10 members of 3 generations of this family.

This new blood factor has a remakably low incidence in the general population since not one reaction was observed in tests of 425 random individuals of groups O and A with the serum of the immunized mother.

With the permission of the affected infant's parents, the new agglutinogen was designated as the Miltenberger blood factor. The abbreviated forms for the gene, factor, and antibody may be represented as *Mi*^{a}, Mi^a, and anti-Mi^a, respectively. The corresponding allelic factor whenever it may be demonstrated can be referred to as Mi^b. The mother of the affected infant had 3 children, all normal at birth and now living and well. The fourth infant, born at term on January 27, 1951 was very pale and somewhat jaundiced. Because of the appearance of dyspnea and more intense jaundice 12 hours after birth, the infant was transferred to the Children's Hospital, where a replacement transfusion with Rh negative blood was carried out. The blood count and hemoglobin values on admission, 2,120,000 and 8 g respectively, were increased to 5,600,000 and 15.2 g. The infant was readmitted at the age of 5 weeks for an additional transfusion and at present there is complete recovery.

Serologic tests on the infant's family with standard antibodies follow:

			Tests with anti-sera				
			D	C	E	c	Mi^a
Father	O	MN	0	0	0	+	+
Mother	A	M	+	+	0	+	0
1st child	A	M	+	+	0	+	+
2nd ''	O	MN	+	+	0	+	0
3rd ''	A	M	+	+	0	+	0
Affected infant	O	MN	+	+	0	+	+
Paternal grandfather*	B		+	+	0	+	0
'' grandmother	O		+	+	0	+	+

* Absence of the factor in this blood and also in that of the father's two siblings was determined by tests with neutralized anti-Mi^a.

Both parents were positive for Fy^a (Duffy), S, and negative for K (Kell) and Le^a (Lewis). The mating was incompatible for the factors Lu^a (Lutheran), Jk^a (Kidd)(1), and N, but antibodies for these factors could not be demonstrated.

Significant results, however, were obtained on testing the mother's serum with the father's red cells. Titration at 37°C with saline suspended cells showed a value of 1:2-1:4, but more distinct effects were found in the indirect anti-globulin test, which showed a titration value of 1:16-1:32. As in the case of anti-Fy^a, the reaction could not be elicited in tests with trypsinized cells(2). The direct Coombs reaction on the infant's cells carried out on the fifth day of life was very weak but this test was performed after a replacement transfusion with group O, Rh negative and presumably Mi^a negative blood. It is safe to assume that the direct Coombs test must have been much stronger at delivery.

The further study of this serum was facilitated by the fact that the only atypical antibody present was anti-Mi^a. This was demonstrated in a series of tests at 18°C with numerous bloods of all antigenic varieties. Under these conditions weak reactions were

1. Allen, F. H., Diamond. L. K., and Niedziela, B., *Nature,* 1951, v167, 402.

2. Cutbush, Marie, Mollison, P. L., and Parkin, D. M., *Nature,* 1950, v165, 188.

obtained only with bloods known to possess the Mi^a factor.

Titrations of anti-Mi^a with the indirect anti-globulin technic on the four positive bloods of the Miltenberger family showed uniform values of 1:16-1:32. Thus, the double-dose effect indicating homozygous individuals could not be demonstrated, but this was not surprising since all four individuals are obviously heterozygous. As is to be expected on the basis of gene frequencies of any factor with such low incidence in the general population, bloods homozygous for the factor must be exceedingly rare, and by the same token the allelic factor Mi^b should be present in almost all bloods tested. Whether or not Mi^a is genetically related to either of the two factors characterized by unusually high incidences, Tj^a (Jay)(3) or k (Cellano)(4) is still to be determined.

Three blood factors of low incidence (Levay)(5), Gr(o), and Jobbins(7) occurring mainly in members of particular families have been reported recently, but their possible relationship to each other and Mi^a cannot be determined because of lack of antibodies for simultaneous studies.*

In contrast to the antibodies for the 3 factors mentioned above, anti-Mi^a is the only one held to be responsible for hemolytic disease and hence is clinically important. Both anti-Mi^a and anti-Gr are the only atypical antibodies present in their respective sera, but they differ from each other since anti-Gr is probably of the naturally occurring variety, its origin by antigenic stimulus of pregnancy or transfusion having been excluded.

The occurrence of antibodies for factors such as Mi^a makes it necessary to exclude their presence in the serum of all instances of hemolytic disease presumed to be due to ABO incompatibility. In this latter group of cases, antibodies reacting only on occasional bloods can be excluded if absorption of the mother's serum with a number of bloods of group A (or B) removes all activity for the father's blood of group A (or B). Only then can one consider the possibility that isoimmunization with resulting hemolytic disease was brought about by the action of anti-A or anti-B.

Summary. A new blood factor, Mi^a, demonstrable with the aid of an immune isoantibody responsible for hemolytic disease of the newborn is briefly described. Its hereditary nature is indicated by its presence in four out of 10 individuals in three generations of a particular family, in contrast to its absence in 425 random bloods.

3. Levine, P., Bobbitt, O. B., Waller, R. K., and Kuhmichel, A. B., PROC. SOC. EXP. BIOL. AND MED., 1951, v77, 403.

4. Levine, P., Wigod, M., Backer, A. B., and Ponder, R., *J. Hemat.*, 1949, v4, 869.

5. Callendar, S. T. and Race, R. R., *Ann. Eugenics*, 1946, v13, 102.

6. Graydon, J. J., *Med. J. Australia*, 1946, v2, 9.

7. Gilbey, B. E., *Nature*, 1947, v160, 362.

* According to Race, anti-Levay cannot be identical with anti-Mi^a since the latter antibody failed to react with blood known to contain the Levay factor. Tests of anti-Mi^a with bloods positive for the Jobbins and Gr factors are still to be made.

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Isoimmunization by a New Blood Factor in Tumor Cells. (18794)

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In the course of preparing a 66-year-old female patient, Mrs. D. S. J., for gastric resection of a tumor later diagnosed as adenocarcinoma, difficulties were encountered in selection of compatible donors.* The patient was in group O, Type MNS, presumably of

* The initial observation on an atypical antibody in the patient's serum was made by Dr. O. B. Bobbitt.