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Genetic Theory of the Rh Blood Types.*

ALEXANDER S. WIENER.

From the Office of the Chief Medical Examiner, New York City, and the Jewish Hospital, Brooklyn.

In a previous paper,[1] a classification of human bloods according to their reactions with 2 principal varieties of anti-Rh agglutinins was proposed, in which 3 sorts of Rh-positive blood are distinguished, designated as Rh_1, Rh_2, and Rh′. Furthermore, it was demonstrated that the 3 most common types, Rh_1, Rh_2, and Rh-negative, are inherited by triple allelic genes, Rh_1, Rh_2, and *rh*. Recently, Wiener and Sonn[2] described a new variety of anti-Rh agglutinin reacting with about 35% of bloods from white individuals in New York City. The agglutinogen detected by this isoantibody proved to be inherited as a simple Mendelian dominant by means of a special gene allelic to ***rh***. With the new agglutinogen the number of subdivisions within the Rh-positive type has been further increased, and the purpose of the present communication is to present a more complete classification and genetic theory in order to include these additional types.

In Table I is presented once more the classification of the 4 types of blood defined by the standard anti-Rh serum of Landsteiner and Wiener,[3] reacting with about 85% of bloods from white individuals, and the anti-Rh_1 serum of Wiener,[4] giving about 70% positive reactions. This table is similar to that given in the previous paper.[1] As Wiener and Landsteiner[1] have pointed out, type Rh_1 and type Rh_2 bear a serologic and genetic relation to each other similar to that of the subgroups A_1 and A_2. For example, the reactions of type Rh_1 blood with the 2 agglutinins anti-Rh and anti-Rh_1 are not due to 2 genetically distinct antigens Rh and Rh_1 in such blood, but to an agglutinogen Rh_1 containing 2 "partial" antigens inherited as a unit by means of a corresponding gene. The analogy

TABLE I.
Relation Between Agglutinins Anti-Rh and Anti-Rh_1.
(Modified after Wiener and Landsteiner.)

		Types of blood and approximate distribution in N.Y.C. (whites)			
Antiserum	Agglutinins in serum	"Rh_1" 67%	"Rh′" 2%	"Rh_2" 18%	"Neg." 13%
Anti-Rh* (standard)	Anti-Rh	Pos.	Neg.	Pos.	Neg.
Anti-Rh_1†	Anti-Rh_1	Pos.	Pos.	Neg.	Neg.
Anti-Rh′‡	Anti-Rh and Anti-Rh_1	Pos.	Pos.	Pos.	Neg.

Quotation marks are used in order to distinguish the 4 types of this table from the more completely classified types of Table IV. Each type in this table includes 2 types of Table IV. For example, the "Neg." type here also includes type Rh″ of Table IV; type "Rh_1" here includes types Rh_1 and Rh_1Rh_2 of Table IV, etc.

* Landsteiner, K., and Wiener, A. S., PROC. SOC. EXP. BIOL. AND MED., 1940, **42**, 223.

† Wiener, A. S., *Arch. Path.*, 1941, **32**, 227; Landsteiner, K., and Wiener, A. S., *J. Exp. Med.*, 1941, **74**, 309.

‡ Wiener, A. S., *Arch. Path.*, 1941, **32**, 227; Levine, P., Burnham, L., Katzin, E. M., and Vogel, P., *Am. J. Obst. and Gyn.*, 1941, **42**, 925.

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1 Wiener, A. S., and Landsteiner, K., PROC. SOC. EXP. BIOL. AND MED., 1943, **53**, 167.

2 Wiener, A. S., and Sonn, E. B., *J. Immunol.*, in press; Wiener, A. S., *Science*, 1943, **98**, 182.

3 Landsteiner, K., and Wiener, A. S., PROC. SOC. EXP. BIOL. AND MED., 1940, **42**, 223.

4 Wiener, A. S., *Arch. Path.*, 1941, **32**, 227.

TABLE II.
Relation Between Agglutinins Anti-Rh and Anti-Rh_2.

Antiserum	Agglutinins in serum	Types of blood and approximate distribution in N. Y. C. (whites) I 32.5%	II 0.5%	III 52.5%	IV 14.5%
Anti-Rh (standard)	Anti-Rh	Pos.	Neg.	Pos.	Neg.
Anti-Rh_2*	Anti-Rh_2	Pos.	Pos.	Neg.	Neg.
Anti-Rh″†	Anti-Rh and Anti-Rh_2	Pos.	Pos.	Pos.	Neg.

*Wiener, A. S., and Sonn, E. B., *J. Immunol.*, in press; Wiener, A. S., *Science*, 1943, **98**, 182.
† Wiener, A. S., unpublished observations. This type of serum is difficult to distinguish from standard anti-Rh serum unless blood of the rare type Rh″ is available.

to the subgroups of A is not complete, however, because rare bloods exist which react with anti-Rh_1 but not anti-Rh agglutinins, and the so-called agglutinogen Rh′ in these bloods, as will be shown presently, is determined by a special allelic gene. The reason why the anti-Rh′ sera (containing both agglutinins anti-Rh and anti-Rh_1) are the most common among the human Rh antisera is that an Rh-negative mother with an erythroblastotic infant of the most frequent type Rh_1 would be apt to possess agglutinins specific for both of the partial antigens in Rh_1 blood. In many anti-Rh′ sera, the strength of the two agglutinins is unequal, and most of the so-called anti-Rh_1 sera are really anti-Rh′ with very weak anti-Rh agglutinins which do not react under the conditions of the test.

As is shown in Table II, the anti-Rh_2 agglutinin of Wiener and Sonn bears a relation to the standard anti-Rh agglutinin entirely analogous to that of the anti-Rh_1 agglutinin. The agglutinogen in blood of type I, like the Rh_1 agglutinogen, appears to possess 2 "partial" antigens, and these are inherited together as a unit by means of a special allelic gene. The rare type II is analogous to type Rh′; it reacts with anti-Rh_2 but not with anti-Rh agglutinins and presumably is also determined by a special allelic gene. Human sera containing anti-Rh_2 agglutinins, as a rule, also contain anti-Rh agglutinins (anti-Rh″ serum of Table II), for reasons already presented; in fact, anti-Rh_2 sera are really anti-Rh″ sera with weak anti-Rh agglutinins.

Incidentally, human sera containing both the agglutinins anti-Rh_1 and anti-Rh_2 have not yet been encountered and such sera must be rare. The reason for this is that Rh-negative mothers cannot have type Rh_1Rh_2 children, although if such a mother has a type Rh_1Rh_2 husband, half the children will be Rh_1 and half Rh_2. At any rate, isoimmunization against both Rh_1 and Rh_2 cannot occur during the same pregnancy. Simultaneous isoimmunization against Rh_1 and Rh_2 could occur, however, in an Rh-negative individual receiving transfusions of type Rh_1Rh_2 blood.

If the reactions of the 3 agglutinins, anti-Rh, anti-Rh_1, and anti-Rh_2, are considered together, five sorts of Rh agglutinogens can be differentiated, each presumably determined by a corresponding allelic gene (*cf.* Table III). These, together with the recessive gene, make up a series of 6 allelic genes, Rh_1, Rh_2, *Rh*, *Rh′*, *Rh″*, and *rh*. As is shown in Table IV, these six genes give rise to 21 theoretically possible genotypes, corresponding to 8 different types of blood, of which, to date, 7 have already been encountered. The eighth type Rh′Rh″ corresponds to the genotype *Rh′Rh″*, the calculated frequency of which is very low. Therefore, it is not surprising that blood giving the reactions of the theoretical type Rh′Rh″ has not yet been found.

Investigations on family material[5] to test this theory of 6 allelic genes have been carried out, and the results in 92 families with 267 children conform with the theoretical expectations. A few illustrative observations will be cited:

(1) In every case where a child possesses agglutinogen Rh_1 or Rh_2, one or both parents also possess the corresponding agglutinogen. Moreover, no instance has yet been encoun-

5 Wiener, A. S., Sonn, E. B., and Belkin, R., *J. Exp. Med.*, in press.

TABLE III.
Variants of the Rh Agglutinogen and Their Corresponding Genes.

Agglutinogen* in erythrocytes	Reactions with Rh Antisera: Anti-Rh	Anti-Rh_1	Anti-Rh_2	Anti-Rh′	Anti-Rh″	Designation of genes*
Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	*rh*
Rh_1	Pos.	Pos.	Neg.	Pos.	Pos.	Rh_1
Rh_2	Pos.	Neg.	Pos.	Pos.	Pos.	Rh_2
Rh	Pos.	Neg.	Neg.	Pos.	Pos.	*Rh*
Rh′	Neg.	Pos.	Neg.	Pos.	Neg.	*Rh′*
Rh″	Neg.	Neg.	Pos.	Neg.	Pos.	*Rh″*

* See foot-note to Table IV.

TABLE IV.
The Eight Rh Blood Types and Their Theoretical Genotypes.

Rh Type* (Phenotype)	Reactions with Rh antisera: Anti-Rh	Anti-Rh_1	Anti-Rh_2	Anti-Rh′	Anti-Rh″	Approximate frequency in N.Y.C. (whites) %	Theoretically possible genotypes*
Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	13.0	*rhrh*
Rh_1	Pos.	Pos.	Neg.	Pos.	Pos.	50.0	Rh_1Rh_1, Rh_1rh, Rh_1Rh, Rh_1Rh', $Rh'Rh$
Rh_2	Pos.	Neg.	Pos.	Pos.	Pos.	15.5	Rh_2Rh_2, Rh_2rh, Rh_2Rh, Rh_2Rh'', $Rh''Rh$
Rh_1Rh_2	Pos.	Pos.	Pos.	Pos.	Pos	17.0	Rh_1Rh_2, Rh_1Rh'', $Rh'Rh_2$
Rh	Pos.	Neg.	Neg.	Pos.	Pos.	2.5	$RhRh$, $Rhrh$
Rh′	Neg.	Pos.	Neg.	Pos.	Neg.	1.5	$Rh'Rh'$, $Rh'rh$
Rh″	Neg.	Neg.	Pos.	Neg.	Pos.	0.5	$Rh''Rh''$, $Rh''rh$
Rh′Rh″	Neg.	Pos.	Pos.	Pos.	Pos.	—†	$Rh'Rh''$

* Knowledge concerning the Rh factors is changing so rapidly that the system adopted in the present paper should only be regarded as provisional and temporary.

† This theoretically possible type has not yet been encountered, which is not surprising considering the extremely low value of the calculated frequency of the genotype $Rh'Rh''$.

tered of a type Rh_1Rh_2 parent with an Rh-negative child or an Rh-negative parent with a type Rh_1Rh_2 child.

(2) An Rh-negative mother and type Rh_1Rh_2 father had 5 Rh_1 and 5 Rh_2 children. According to the theory, this father belongs to genotype Rh_1Rh_2, and as expected, half the children belong to genotype Rh_1rh and half to genotype Rh_2rh.

(3) In 2 families Rh_1 × Rh-negative, there was a total of 7 type Rh_1 and 5 Rh-negative children. Here the Rh_1 parents obviously belong to genotype $Rh_1\ rh$.

(4) In a family Rh_1 × Rh_1, there were 3 Rh_1 and 2 Rh′ children. Here, evidently, one of the Rh_1 parents belongs to genotype Rh_1Rh', the other to genotype Rh_1Rh' or genotype Rh_1rh.

(5) Families $Rh_1 \times Rh_1$ and $Rh_1 \times$ Rh-negative have been encountered in which the children belonged either to type Rh_1 or type Rh. In these families one or both of the Rh_1 parents must belong to genotype Rh_1Rh.

(6) In a Negro family, the husband belonged to type Rh′, the child to type Rh_2 while the wife was Rh-negative, in conflict with the heredity theory. However, the husband was actually not the father of the child because he belonged to type N and the child to type M.

These examples suffice to illustrate how the theory operates and the complete family data will be presented in detail in a separate publication.[5]

An interesting consequence of the theory is that an antigen resulting from the action of a single gene may be indistinguishable serologically from that produced by the combined action of two allelic genes. Thus, gene Rh_1 alone produces the same effect as genes *Rh* and *Rh′* together, and gene Rh_2 produces the same effect as genes *Rh* and *Rh″* together. The only way to differentiate the two cases is by family studies. For example, in the mating Rh-negative $\times$ Rh_2, if the Rh_2 type is determined by gene Rh_2, in some families all the children will belong to type Rh_2, while in other families half the children will be Rh_2 and half Rh-negative (or type Rh). On the other hand, in matings Rh-negative $\times$ Rh_2 where the Rh_2 parent belongs to genotype *RhRh″*, half the children will belong to type Rh and half to type Rh″.

The Rh blood types should prove useful in forensic medicine for criminal identification because they multiply the number of individual differences in human blood. Moreover, the Rh types offer the prospect of increasing substantially the chances of exclusion in cases of disputed parentage.

In typical cases of erythroblastosis where the mother is Rh-negative and the father is Rh-positive, if the father belongs to type Rh_1Rh_2 the prognosis for future pregnancies is poor because every child must be Rh-positive (either type Rh_1 or type Rh_2). Moreover, should specific desensitization prove feasible as a method of preventing erythroblastosis, it might be found essential to use Rh antigens of the same variety as that to which the mother has been sensitized.

In conclusion, it should be mentioned that the number of Rh types existing is not limited to those described in this paper. For example, occasionally bloods are encountered which give intermediate reactions, and rare bloods have been found which give atypical reactions.

Summary. Three varieties of anti-Rh agglutinins have been encountered, designated as anti-Rh (standard), anti-Rh_1, and anti-Rh_2, and agglutinating, respectively, approximately 85%, 70%, and 35% of bloods from white individuals in New York City. Human sera containing agglutinins anti-Rh and anti-Rh_1 together are designated anti-Rh′; sera containing the two agglutinins anti-Rh and anti-Rh_2 are designated anti-Rh″. By means of the 3 sorts of Rh agglutinins, 5 varieties of Rh agglutinogens are demonstrable, designated as Rh_1, Rh_2, Rh, Rh′, and Rh″. These in combination give rise to 8 Rh blood types (including the Rh-negative type), of which all but one, the rarest, have actually been encountered. A theory to explain the heredity of the Rh blood types is proposed in which the existence of 6 allelic genes is postulated. Evidence in support of the theory is presented and some of the implications of the theory are mentioned.