HEREDITY OF THE Rh BLOOD TYPES*

II. Observations on the Relation of Factor Hr to the Rh Blood Types

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In a previous paper (1), data were presented regarding the heredity of the Rh blood types and their distribution in the general population, confirming the accuracy of the theory of six allelic genes (2). In the present paper, we propose to report the results of investigations of the relationship of factor Hr (Levine and Javert (3)) or St (Race and Taylor (4)) to the Rh blood types.

Nomenclature and Genetic Theory

Advances in the knowledge of the Rh blood types have made possible certain improvements in the nomenclature (5), as a result of which the designations of Rh types correspond more closely with the antisera with which they react. The standard anti-Rh agglutinin, which clumps the blood of about 85 per cent of white individuals, is now designated anti-Rh_o. The agglutinin reacting with approximately 70 per cent of bloods from white individuals is now designated anti-Rh′ instead of anti-Rh_1, and the agglutinin giving 30 per cent positive reactions is called anti-Rh″ instead of anti-Rh_2. With regard to the Rh types, bloods reacting with agglutinin anti-Rh_o but not anti-Rh′ or anti-Rh″ are designated type Rh_o instead of type Rh. The names of types Rh′, Rh″, and Rh′Rh″ remain unchanged. The name of type Rh_1 is retained but this type now has the alternative designation Rh_o', and similarly type Rh_2 may also be called Rh_o'', and type Rh_1Rh_2 may also be called $Rh_o'Rh_o''$. The terms Rh_o', Rh_o'', and $Rh_o'Rh_o''$ are to be used whenever necessary for the sake of clarity or to avoid ambiguity, but ordinarily the simpler designations Rh_1, Rh_2, and Rh_1Rh_2 will still be found preferable.

The six standard genes, and the reactions which they determine are presented once more in Table I, using the new nomenclature. This scheme has been confirmed by Race *et al.* (6) working independently in England, and these workers have also defined the reactions of each antigen with anti-Hr (or anti-St) serum. For example, gene *rh* determines a blood property which reacts with anti-Hr serum but not with anti-Rh_o, anti-Rh′, or anti-Rh″; gene Rh_1 determines a property reacting with anti-Rh_o and anti-Rh′, but not with anti-Rh″ or anti-Hr; etc. It will be seen that each of the

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properties determined by the six genes can be differentiated using the three sera, anti-Rh_o, anti-Rh′, and anti-Rh″, alone. The anti-Hr serum is not essential for the diagnosis although it defines an additional characteristic of each blood property. As is pointed out elsewhere (2, 7) occasionally bloods are encountered which give intermediate reactions, indicating the existence of Rh genes in addition to the six standard allelic genes. A few of these "intermediate genes" are listed in Table I, but for the sake of simplicity the aberrant types which they determine will not be discussed further here.

As has already been shown in previous reports (1, 2) the six standard allelic genes give rise to 21 genotypes. The expected reactions of the bloods from individuals belonging to each of these genotypes are given in Table II, these reactions having been

TABLE I

The Rh Series of Genes

Designations of genes	Reactions with Rh antisera			Reaction with anti-Hr serum
	Anti-Rh_o	Anti-Rh′	Anti-Rh″	
Standard genes				
rh	Neg.	Neg.	Neg.	Pos.
Rh_o	Pos.	Neg.	Neg.	Pos.
Rh′	Neg.	Pos.	Neg.	Neg.
Rh″	Neg.	Neg.	Pos.	Pos.
Rh_1	Pos.	Pos.	Neg.	Neg.
Rh_2	Pos.	Neg.	Pos.	Pos.
Some of the "intermediate" genes				
Rh_1^{-}	Pos.	Pos.	Weak	Neg.
Rh_2^{-}	Pos.	Weak	Pos.	?
Rh′′	Weak	Pos.	Neg.	?
Rh″′	Weak	Neg.	Pos.	?

arrived at simply by combining (with the aid of Table I) the effects of the two genes making up the genotype. According to the experience of the authors (8), a "double dose" of a gene such as Rh_1 or Rh_2 does not change appreciably the strength of the reactions with agglutinins anti-Rh′ or anti-Rh″, respectively, so that, for example, bloods from individuals of genotypes Rh_1Rh_1 and Rh_1rh cannot be differentiated reliably with the aid of anti-Rh′ serum alone. On the other hand, the strength of the reactions with anti-Hr sera is affected by the "gene dose" as shown in Table II. For example, bloods from genotypes Rh_2rh and *rhrh* give strong reactions with anti-Hr serum; genotypes Rh_1rh and Rh_1Rh_2 give only moderate or weak reactions; while genotypes Rh_1Rh_1 and Rh_1Rh' give negative reactions. This suggests that there is some fundamental difference between the Hr factor and the various Rh factors (9), perhaps similar to the difference postulated by Wiener and Karowe (10) between property O and agglutinogens A and B.

If one takes into account the reactions of agglutinins anti-Rh_o, anti-Rh′, and anti-Rh″, and disregards anti-Hr, the 21 genotypes fall into eight phenotypes, as shown in

Table II. These eight Rh blood types make up four natural pairs, giving rise to four classes, analogous to the four blood groups, as shown in Table III. The distributions of the Rh blood types and classes among white and colored individuals in New York City are also summarized in Table III. The Hr reactions serve to subdivide further

TABLE II

The Eight Standard Rh Types and Their Reactions

Rh blood type	Reactions with Rh antisera			Genotypes	Expected rection with anti-Hr serum
	Anti-Rh_o	Anti-Rh′	Anti-Rh″		
Negative	Neg.	Neg.	Neg.	*rhrh*	Strong
$Rh_1(Rh'_o)$	Pos.	Pos.	Neg.	*Rh_1Rh_1* *Rh_1Rh'*	Neg.
				Rh_1rh *Rh_1Rh_o* *$Rh'Rh_o$*	Weak
$Rh_2(Rh''_o)$	Pos.	Neg.	Pos.	*Rh_2Rh_2* *Rh_2Rh''* *Rh_2rh* *Rh_2Rh_o* *$Rh''Rh_o$*	Strong
Rh_1Rh_2 ($Rh_oRh''_o$)	Pos.	Pos.	Pos.	*Rh_1Rh_2* *Rh_1Rh''* *$Rh'Rh_2$*	Weak
Rh_o	Pos.	Neg.	Neg.	*Rh_oRh_o* *Rh_orh*	Strong
Rh′	Neg.	Pos.	Neg.	*Rh′Rh′* *Rh′rh*	Neg. Weak
Rh″	Neg.	Neg.	Pos.	*Rh″Rh″* *Rh″rh*	Strong
Rh′Rh″	Neg.	Pos.	Pos.	*Rh′Rh″*	Weak

class U (types Rh_1 and Rh′), increasing the number of recognizable phenotypes to ten (*cf.* Table II).

We should like to take this opportunity to clarify some loose statements which have appeared in the literature. Reports from England imply that it is now possible to determine directly the Rh genotypes of almost 90 per cent of the population. Perusal of Table II shows, however, that of the phenotypes differentiated by sera anti-Rh_o, anti-Rh′, anti-Rh″, and anti-Hr, all but four of the ten different types include two or more genotypes, so that, actually, the genotype of only 15 per cent of the population

can be recognized directly by serological tests alone. If the Rh types of other members of the family are known, to be sure, the exact genotype of the individual may be ascertained indirectly, or if one disregards the rarer genotypes such as $Rh'Rh'$, $Rh''Rh''$, Rh_1Rh', etc., one can make a pretty good guess as to an individual's genotype. It is probably in the last mentioned sense that the statement was intended.

It has also been stated that with anti-Hr sera it is possible to differentiate homozygous and heterozygous individuals of type Rh_1, so that the test can be applied for giving a more precise prognosis for future pregnancies to a couple who have had an erythroblastotic baby. Here the implication seems to be that when the woman is Rh-negative and her husband is type Rh_1, Hr-negative, all their children will be Rh-positive (type Rh_1) and therefore subject to the disease, while if the husband is

TABLE III

Classification of Rh Blood Types and Distribution among Whites and Negroes in New York City

Classes	Bloods lacking Rh_o factor						Bloods containing Rh_o factor					
	Reaction with antisera			Designation of types	Distribution		Reaction with antisera			Designation of types	Distribution	
	Anti-Rh_o	Anti-Rh′	Anti-Rh″		Whites*	Negroes‡	Anti-Rh_o	Anti-Rh′	Anti-Rh″		Whites*	Negroes‡
					per cent	*per cent*					*per cent*	*per cent*
W	−	−	−	Neg.	12.9	8.1	+	−	−	Rh_o	2.6	41.2
U	−	+	−	Rh′	0.9	2.7	+	+	−	Rh_1	54.1	20.2
V	−	−	+	Rh″	0.3	—	+	−	+	Rh_2	12.8	22.4
UV	−	+	+	Rh′Rh″	—	—	+	+	+	Rh_1Rh_2	16.4	5.4

* Based on 1000 tests. Calculated gene frequencies: rh = 35.9 per cent; Rh_1 = 43.4 per cent; Rh_2 = 13.7 per cent; Rh_o = 3.5 per cent; Rh' = 1.2 per cent; Rh'' = 0.4 per cent. D = 100 − ΣRh_i = 100 − 98.1 = +1.9 per cent.

‡ Based on tests on 223 negroes from Harlem Hospital. Calculated gene frequencies: rh = 28.4 per cent; Rh_1 = 11.7 per cent; Rh_2 = 14.4 per cent; Rh_o = 42.1 per cent; Rh' = 2.7 per cent. D = 100 − ΣRh_i = 100 − 99.3 = +0.7 per cent.

type Rh_1, Hr-positive, half of the children will be Rh-negative and therefore normal. As a matter of fact, type Rh_1, Hr-negative includes the two genotypes Rh_1Rh_1 and Rh_1Rh', while type Rh_1, Hr positive includes three genotypes, Rh_1Rh_o, $Rh'Rh_o$ and Rh_1rh (*cf.* Table II). Therefore, in some matings Rh-negative × Rh_1 (Hr+) none of the children can be Rh-negative; *e.g.*, when the Rh_1 parent belongs to genotype Rh_1Rh_o or $Rh'Rh_o$. The statement holds only if one disregards the rare genotypes, Rh_1Rh', Rh_1Rh_o, and $Rh'Rh_o$, and this is probably what was intended. With regard to the four classes, Hr serum subdivides class U into the homozygous class U, Hr-negative (genotype UU) and the heterozygous class U, Hr-positive (genotype UW).

The impression has become prevalent that in cases of erythroblastosis caused by incompatibility with regard to the Hr factor, the mother is Rh-positive and the affected infant Rh-negative. If the Hr factor is responsible, the mother must be Hr-negative, while the father and infant are Hr-positive. The child cannot possibly

be Rh-negative, because it must inherit either gene Rh_1 or gene Rh' from its mother. The Hr factor can only be involved in cases of erythroblastosis where the mother belongs to type Rh_1 (or, very rarely, to type Rh′, genotype $Rh'Rh'$), and the child does not belong to type Rh_2, Rh″, Rh_o, or Rh-negative. There is no restriction in these cases as to the Rh type of the father, because Hr-positive individuals occur in all the eight Rh types (*cf.* Table II).

Standardization of Sera; Technique of Tests

Sera containing any one of the three agglutinins, anti-Rh_o, anti-Rh′, or anti-Rh″, alone can readily be identified because of the wide differences in the incidence of positive reactions among white individuals, namely, 85, 70, and 30 per cent, respectively. Difficulties have arisen because some sera contain two of the three primary agglutinins: namely, sera anti-Rh_oRh' (or anti-Rh'_o) contain the standard anti-Rh_o agglutinin together with anti-Rh′ and give about 87 per cent positive reactions; while sera anti-Rh_oRh'' (or anti-Rh''_o) contain agglutinins anti-Rh_o and anti-Rh″ together and give about 85.5 per cent positive reactions. Formerly, anti-Rh_o, anti-Rh'_o, and anti-Rh''_o sera were difficult to differentiate unless bloods of the rare types Rh′ and Rh″ were available, because absorbing the sera in order to separate the agglutinins is a difficult procedure. With the aid of blocking anti-Rh_o sera (11), however, the problem of standardizing anti-Rh sera has been considerably simplified. As has been pointed out elsewhere (11), if bloods of types Rh_1, Rh_2, and Rh_1Rh_2 are treated with blocking anti-Rh_o sera, they lose their capacity to react with anti-Rh_o agglutinins. The artificial Rh′, Rh″, and Rh′Rh″ cells resulting in this way can be used for standardizing new Rh antisera.

For Rh typing, sera containing anti-Rh′ or anti-Rh″ agglutinin alone are obviously far more valuable than sera anti-Rh'_o or anti-Rh''_o. Attempts to convert anti-Rh'_o sera into anti-Rh′ by absorption with blood cells containing antigen Rh_o but lacking Rh′, *e.g.* type Rh_2 or Rh_o, have not been consistently successful. In some cases, the anti-Rh_o agglutinin seemed to get stronger instead of weaker after the absorption, and the reason for this has become clear following the discovery of the existence of blocking antibodies. Apparently such anti-Rh'_o sera contain weak anti-Rh_o blocking antibodies which are absorbed more readily than the anti-Rh_o agglutinin. In fact, some of the natural anti-Rh′ sera appear to be more complicated rather than simpler than anti-Rh'_o sera (12). The anti-Rh′ serum used in our studies and described in the previous paper, for example, was found to contain at least three antibodies, namely, agglutinins anti-Rh′ and anti-Rh_o together with weak anti-Rh_o blocking antibodies. The anti-Rh_o blocking antibodies masked the anti-Rh_o agglutinin, so that in the tests the serum behaved as if it contained the agglutinin anti-Rh′ alone. This suggests the use of anti-Rh_o blocking sera for converting anti-Rh'_o and anti-Rh''_o sera into anti-Rh′ and anti-Rh″, respectively. In this way, for example, the anti-Rh'_o serum used in our investigations has been successfully converted into an anti-Rh′ reagent with the aid of a potent anti-Rh_o blocking serum (titer 64). As an example, we cite the following formula which gave satisfactory results with our anti-Rh'_o serum: 1 part of the stock group O, anti-Rh'_o serum was mixed with 1 part each of boiled group A_1 and group B saliva from secretors (or 2 parts Witebsky's solution of purified group substances), 2 parts of anti-Rh_o blocking serum, and 5 parts of saline solution.

The anti-Hr serum used in the present study came from a group A, Rh-positive mother who had had an erythroblastotic infant.[1] This serum had a maximum titer of only 10 to 20 and was much less potent than our standard Rh antisera. For the tests, the serum was used in a 1:3 dilution, one part of serum being mixed with one part of group B saliva (from secretors) or Witebsky's group substance and one part saline solution The serum deteri-

[1] The clinical data of this case will be presented in a separate paper.

orated rather quickly, so that later in the study, it was necessary to omit the saline solution from the mixture. Eventually the serum dropped so markedly in titer that it gave distinct reactions only with the more sensitive bloods, namely, bloods of types Rh_2, Rh″, Rh_o, and Rh-negative, while less sensitive bloods of types Rh_1Rh_2 and Rh_1 no longer were clumped by the serum. This property of the serum may serve to explain the difference in percentage of positive reactions reported between the Hr serum of Levine and Javert and the St serum of Race and Taylor.

Statistical Considerations

Race and Taylor's theory concerning the Hr factor can be tested by the investigations of families, or by analyzing the distribution of the Hr factor and the Rh types in the general population. In the present paper, we propose to test the theory with the aid of data of the latter type.

One could conceive that the Hr factor is inherited by a pair of genes *Hr* and *hr*. Then under Race and Taylor's theory,

$$Hr = Rh_2 + Rh'' + Rh_o + rh = V + W \quad (1)$$

$$hr = Rh_1 + Rh' = U \quad (2)$$

If the Hr reactions and Rh types are determined for a random series of individuals, then the three genotypes, *HrHr*, *Hrhr*, and *hrhr* can be recognized directly, because

$$hrhr = Rh_1(Hr^-) + Rh'(Hr^-) = U(Hr^-) \quad (3)$$

$$Hrhr = Rh_1(Hr^+) + Rh'(Hr^+) + Rh_1Rh_2 + Rh'Rh'' = U(Hr^+) + UV \quad (4)$$

and

$$HrHr = \text{Rh-negative} + Rh_o + Rh_2 + Rh'' = W + V \quad (5)$$

The theory can be tested, just like Landsteiner and Levine's theory of inheritance of the MN types,[2] by determining how closely the following relation holds (2):

$$\sqrt{U(Hr^-)} + \sqrt{V + W} = 1 \quad (6)$$

The theory can also be tested by the χ^2 method as follows:—

If x and y represent the frequencies of genes *Hr* and *hr*, respectively, then

$$x = V + W + \frac{U(Hr^+) + UV}{2} \quad (7)$$

$$y = U(Hr^-) + \frac{U(Hr^+) + UV}{2} \quad (8)$$

From these values the expected frequencies of the three genotypes can be calculated with the aid of the formulae:

$$HrHr = x^2$$

$$Hrhr = 2xy$$

$$hrhr = y^2$$

and χ^2 is then computed in the usual manner, by comparing the observed with the expected frequencies.

RESULTS

In Table IV, are summarized our observations of the Hr factor and Rh blood types among 124 white individuals and 49 negroes in New York City.

[2] Genes *Hr* and *U* are allelic under this theory in the same way as genes *M* and *N*.

It will be seen that in conformity with expectations there were no Hr-negative individuals except in type Rh_1. Moreover, the reactions given by bloods of types Rh_2, Rh_o, and Rh-negative, were almost uniformly strong, while Hr-positive bloods of types Rh_1 and Rh_1Rh_2 on the whole gave only weak or moderate reactions.

TABLE IV

Reactions of Anti-Hr Sera with Bloods of the Various Rh Blood Types

Rh types	Tests on white individuals				Tests on negroes			
	Total No. examined	Reactions with anti-Hr serum			Total No. examined	Reactions with anti-Hr serum		
		Negative	Weak positive	Strong positive		Negative	Weak positive	Strong positive
Neg.	18	0	0	18	7	0	0	7
Rh_1	75	33	32	10	9	1	6	2
Rh_2	11	0	1	10	12	0	0	12
Rh_1Rh_2	14	0	9	5	1	0	1	0
Rh_o	2	0	2	0	18	0	0	18
Rh′	3	0	2	1	2	0	0	2
Rh″	1	0	0	1	—	—	—	—
Totals	124	33	46	45	49	1	7	41

TABLE V

χ^2 Test of Race and Taylor's Genetic Theory of the Hr Factor

Population tested	No. examined	Genotype *hrhr* U (Hr^-)		Genotype *Hrhr* U (Hr^+) + UV		Genotype *HrHr* W + V		χ^2	P
		Observed	Expected	Observed	Expected	Observed	Expected		
Whites	124	33	31.5	59	62.0	32	30.5	0.28	0.61
Negroes	49	1	0.6	9	9.8	39	38.6	0.29	0.61

In Table V, we have regrouped our data under the three genotypes, *HrHr*, *Hrhr*, and *hrhr*.

For the series of white individuals,[3]

$$\sqrt{U(Hr^-)} + \sqrt{W + V} = \sqrt{0.2661} + \sqrt{0.2581} = 0.5158 + 0.5080 = 102.4 \text{ per cent}$$

$$D = 100 - 102.4 = -2.4 \text{ per cent}$$

$$P.E._D = \pm \frac{0.6745}{2\sqrt{124}} = \pm 3.0 \text{ per cent}$$

Since the deviation is less than its probable error, these results agree satisfactorily with the expectations under the theory.

[3] For derivation of formula for $P.E._D$, see Wiener (13).

For the series of bloods from negroes,

$$D = 1 - (\sqrt{.0208} + \sqrt{0.7917}) = -3.4 \text{ per cent}$$

$$P.E._D = \pm \frac{0.6745}{2\sqrt{48}} = \pm 4.9 \text{ per cent}$$

Therefore, here also the results conform with the expectations under the theory.

As shown in Table V, similar satisfactory results were obtained using the χ^2 method.

A third method of testing the theory is to compare the incidence of the Hr-negative type in the population with that calculated from the frequencies of the genes Rh_1 and Rh'.

Since the Hr-negative type is identical with genotype UU,

$$\text{Hr-negative} = (U)^2 = (Rh_1 + Rh')^2$$

From Table III, we have:

For white individual, Hr-negative $= (0.434 + 0.012)^2 = 19.9$ per cent

For negroes, Hr-negative $= (0.117 + 0.027)^2 = 2.1$ per cent

TABLE VI

Frequency of Hr-Negative Bloods among Negroes and White Individuals

Blood of	No. tested	Hr reaction			
		Negative		Positive	
		No.	Per cent	No.	Per cent
Whites					
Series *a* (Table V)	124	33	26.6	91	73.4
Series *b*	115	34	29.6	81	70.4
Totals	239	67	28.0	172	72.0
Negroes					
Table V	49	1	2.0	48	98.0

As shown in Table VI, the observed frequency of the Hr-negative type in negroes agrees closely with the expected value. The observed frequency of Hr-negative bloods in the series of white individuals is somewhat high. The discrepancy is probably due mainly to chance; *e.g.*, the series a from Table V contains a higher percentage of type Rh_1 individuals than the series cited in Table III. In addition, bloods giving weak reactions with anti-Hr sera are far more common among white individuals than among negroes, so that false negative reactions are more apt to occur in tests on bloods from white individuals, as has already been pointed out (*cf.* page 68).

DISCUSSION

The factors Hr and P have very similar distributions among white and negro individuals in New York City. Among white persons approximately 25 per cent are negative for Hr and P, while among negroes the incidence of negative reactions is only 2 per cent for both factors. Moreover, bloods from negroes give strong reactions with the two antisera more frequently than bloods from

whites. Yet the two factors Hr and P are independent of each other, as was proved when a series of blood samples was tested for P, Hr, and the Rh types simultaneously (8). This serves to emphasize the fact that parallel tests must be performed, before one can assert with certainty that two antisera are identical, because two sera can give the same percentage of positive reactions merely by coincidence.

The Hr factor is important because it seems to be the property most often involved in the cases of hemolytic disease where the mother is Rh-positive, and hemolytic transfusion reactions in Rh-positive patients. It should be suspected whenever the mother of an erythroblastotic baby proves to belong to type Rh_1. Another rarer possibility in such instances is that the mother may have become sensitized to factor Rh″, lacking from blood of type Rh_1. The latter possibility can be excluded, if the father of the infant does not belong to type Rh_2, Rh_1Rh_2, or Rh″. Should the type Rh_1 mother of an erythroblastotic infant require a blood transfusion, a biological test should first be tried with Hr-negative blood. If the result of the test is negative, any quantity of the same blood can be transfused safely; if the result of the test is positive, a biological test with Rh-negative blood should next be tried. For transfusing infants with hemolytic disease, where the mother is Rh-positive, the safest procedure is to use the mother's washed red cells suspended in compatible plasma. When the mother (belonging to type Rh_1) is too ill to act as donor, Hr-negative blood should be tried for transfusing the infant. If the response is unsatisfactory, Rh-negative blood should be transfused.

It is evident that a complete blood donor service should have available at least a few Hr-negative donors of each blood group, in order to be able to cope with problem cases. Unfortunately, the necessary sera are difficult to obtain, and those which have been available to date give such weak reactions that the results are reliable only in the hands of experts. For the same reasons, the Hr factor will probably have only limited application in forensic medicine for individual identification and in cases of disputed parentage.

SUMMARY

1. The theory of six allelic genes is reviewed, using the new improved nomenclature, and data are summarized regarding the distributions of the eight Rh types among white and negro individuals in New York City.

2. Results are presented of tests for property Hr in a series of 239 white individuals and 49 negroes. Statistical analysis of these data yields results supporting Race and Taylor's hypothesis that anti-Hr sera react with the blood properties determined by the genes Rh_2, Rh'', Rh_0, and rh, but not with the factors determined by genes Rh_1 and Rh'.

3. The practical importance of the Hr factor is discussed.

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