14234

Heredity of Variants of the Rh Type.*

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By immunizing animals with the blood of rhesus monkeys, Landsteiner and Wiener[1] obtained antisera which agglutinated approximately 85% of human bloods from white individuals in New York City, independently of the blood groups and other known agglutinogens. The agglutinable property in human blood responsible for the reaction was designated as Rh. Subsequently sera giving parallel reactions were obtained from patients who had had hemolytic reactions to blood transfusions of a homologous group[2] and from mothers of erythroblastotic babies.[3] Among the human sera two varieties were found, one of which, the more common, gave about 3% more positive reactions.[4]

Furthermore, some human anti-Rh sera were encountered which agglutinated only about 70% of human bloods,[5] that is, only about five-sixths of the Rh positive bloods, so that a major subdivision within the Rh positive type was demonstrated. Human sera of this type are rather uncommon.

In place of the nomenclature suggested by one of the writers,[6] the following less complicated designations are now suggested (cf.

TABLE I.
Classification of the Subtypes of Rh.

Anti-Rh serum	Designation of agglutinin in serum	Approximate % positive reactions	Reactions of various bloods among white individuals (New York City)			
			About 70%	About 3%	About 14%	About 13%
1.*	Anti-Rh	84	Pos.	Neg.	Pos.	Neg.
2.†	Anti-Rh_1	73	"	Pos.	Neg.	"
3.‡	Anti-Rh′	87	"	"	Pos.	"
	Designation of types		Rh positive			Rh negative
	Designation of main subtypes			Rh_1 (Rh′)	Rh_2	

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

2 Wiener, A. S., and Peters, H. R., *Ann. Int. Med.*, 1940, **13**, 2306.

3 Levine, P., Burnham, L., Katzin, E. M., and Vogel, P., *Am. J. Obst. and Gyn.*, 1941, **42**, 925.

4 The immune anti-rhesus sera from guinea pigs correspond to the human antisera giving about 84% positive reactions with bloods from N. Y. white individuals, as will be shown in a separate publication (Landsteiner, K., and Wiener, A. S., in preparation). However, it may be noted that these human sera are apparently not entirely identical in their reactions.

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

6 Wiener, A. S., *Blood Groups and Transfusion*, p. 254, C. C. Thomas, Springfield, Ill., 1943.

Table 1). When a distinction between the various subtypes of Rh is desired, the great majority of bloods, namely, those which react also with serum No. 2 of the table, are designated as Rh_1. Of these, a small percentage fail to react with guinea-pig antisera or human sera listed as No. 1 and are designated as Rh.' Those bloods which do not react with sera anti-Rh_1 (No. 2) are called Rh_2. The agglutinins are named so as to correspond to agglutinogens of the blood cells. The new nomenclature described above is suggested with the approval of Dr. Philip Levine.

Bloods of subtype Rh_2 may give weaker re-

TABLE II.
List of Family Material.

Family No.*	Parents: Father	Parents: Mother	Children				
1	OMNRh$_1$	OMNRh$_1$	OMRh$_1$ ♀	OMRh$_1$ ♂	OMNRh$_1$ ♂	OMRh$_1$ ♀	
2	OMNRh$_1$	OMNRh$_1$	ONRh$_1$ ♂	OMNRh$_1$ ♂	OMNRh$_1$ ♂		
3	OMNRh$_1$	BMNRh–	BMNRh$_2$ ♂	ONRh$_1$ ♂	BMNRh$_2$ ♂	BNRh$_2$ ♂	
4	OMRh$_1$	BNRh$_1$	BMNRh$_2$ ♂	OMNRh$_2$ ♂	OMNRh$_1$ ♀	OMNRh$_2$ ♀	
5	OMNRh$_1$	**A$_1$NRh$_1$**	ONRh$_1$ ♂	OMNRh$_1$ ♀	OMNRh$_1$ ♂		
6	BMRh$_1$	OMNRh$_1$	OMRh$_1$ ♀	BMNRh$_1$ ♀	OMNRh$_1$ ♀	BMRh$_1$ ♂	
7	A$_2$MNRh$_1$	BMRh$_1$	A$_2$MRh$_1$ ♀	BMRh$_1$ ♀			
8	A$_1$MNRh–	OMNRh$_1$	A$_1$MRh$_1$ ♀				
9	A$_2$MNRh–	A$_2$MRh$_2$	A$_2$MRh$_2$ ♀	A$_2$MRh$_2$ ♂	A$_2$MRh$_2$ ♀	A$_2$MNRh$_2$ ♀	
10	A$_1$MRh$_1$	A$_1$MRh$_2$	A$_1$MRh$_1$ ♀	A$_1$MRh– ♀			
11	A$_1$MRh$_2$	OMRh$_1$	OMRh$_2$ ♂	A$_1$MRh$_1$ ♂	A$_1$MRh$_2$		
12	A$_1$MNRh$_1$	ONRh–	**A$_1$MNRh– ♂**	A$_2$MNRh$_1$			
13	A$_1$NRh$_1$	A$_1$MNRh$_2$	A$_1$MRh$_2$ ♀ † A$_1$MNRh$_1$ ♂	A$_1$MNRh$_1$ ♀	A$_1$NRh$_1$ ♀	A$_1$MNRh$_1$ ♂	A$_1$NRh$_2$ ♀
14	OMRh–	OMRh$_1$	OMRh$_1$ ♂	OMRh$_1$ ♂			
15	OMRh$_1$	OMNRh$_1$	OMRh$_1$ ♀	OMNRh$_1$ ♀	OMNRh$_1$ ♀		
16	A$_2$MRh$_2$	BNRh$_1$	OMNRh– ♀	A$_2$BMNRh$_1$ ♂	BMNRh$_1$ ♂		
17	OMRh$_1$	OMNRh$_2$	OMNRh$_1$ ♂	OMRh$_1$ ♂	OMNRh$_1$ ♀		
18	OMNRh$_1$	OMRh$_1$	OMNRh$_1$ ♀	OMNRh$_1$ ♂	OMNRh$_1$ ♂		
19	A$_1$MNRh$_1$	A$_1$NRh$_1$	A$_1$NRh$_1$ ♂				
20	OMRh$_1$	A$_1$MRh–	A$_1$MRh$_2$ ♀ A$_1$MRh$_1$ ♂	A$_1$MRh$_1$ ♂ A$_1$MRh$_2$ ♂	A$_1$MRh$_2$ ♀ A$_1$MRh$_1$ ♀	A$_1$MRh$_1$ ♂ A$_1$MRh$_2$ ♂	A$_1$MRh$_2$ ♀ A$_1$MRh$_1$ ♂
21	BMNRh$_1$	A$_1$NRh$_2$	OMNRh$_1$ ♂	BNRh$_1$ ♀			
22	A$_1$MRh$_1$	A$_1$NRh$_1$	A$_1$MNRh$_1$ ♀	A$_1$MNRh$_1$ ♀	A$_1$MNRh$_2$ ♀	OMNRh$_1$ ♂	
23	A$_1$MNRh$_2$	BMRh$_1$	A$_1$MNRh$_1$ ♂	A$_1$BMNRh$_1$ ♂			
24	A$_1$MRh$_1$	A$_1$MRh$_1$	A$_1$MRh$_1$ ♀	A$_1$MRh$_1$ ♀			
25	OMRh$_1$	OMNRh$_1$	OMNRh$_1$ ♂	OMRh$_1$ ♀	OMNRh$_1$ ♀		
26	OMRh$_2$	OMRh$_2$	OMRh$_2$ ♂	OMRh$_2$ ♀			
27	A$_1$BNRh–	ONRh–	BNRh– ♂	BNRh– ♂			
28	A$_2$MRh$_1$	OMNRh$_1$	A$_2$MRh$_1$ ♂	A$_2$MNRh$_1$ ♀	OMNRh– ♀		
29	A$_1$MRh$_1$	A$_2$MNRh$_1$	A$_2$MNRh– ♀	A$_1$MRh$_1$ ♂	OMRh$_1$ ♀		
30	OMRh$_1$	ONRh–	OMNRh$_1$ ♂	OMNRh$_1$ ♀			
31	BNRh$_1$	OMNRh$_1$	OMNRh$_1$ ♀	OMNRh$_1$ ♂	ONRh– ♀	ONRh$_1$ ♂	ONRh– ♀
32	A$_1$NRh$_1$	OMRh$_1$	OMNRh$_1$ ♀	OMNRh$_1$ ♀			
33	OMNRh$_1$	OMRh$_1$	OMNRh– ♀	OMRh$_1$ ♀			
34	OMNRh$_1$	BMNRh$_1$	BNRh$_1$ ♂	OMRh$_1$ ♀			
35	BNRh$_1$	A$_2$MRh$_1$	OMNRh$_1$ ♀	A$_2$MNRh– ♂	BMNRh$_1$ ♀		
36	A$_1$MNRh$_2$	OMNRh$_1$	A$_1$MNRh$_1$ ♂	A$_1$NRh$_1$ ♂			
37	BNRh$_1$	BMRh$_1$	BMNRh$_1$ ♂	BMNRh$_1$ ♂	BMNRh$_1$ ♀	OMNRh$_1$ ♂	
38	OMNRh$_1$	A$_1$MNRh$_1$	A$_1$NRh$_1$ ♂	A$_1$MNRh$_1$ ♀			
39	A$_1$NRh$_1$	OMNRh$_1$	A$_1$MNRh$_1$ ♀	OMNRh$_1$ ♂	A$_1$MNRh$_1$ ♀		
40	A$_2$BNRh–	OMNRh$_1$	BMNRh$_2$ ♀				
41	ONRh$_1$	OMNRh–	OMNRh$_1$ ♂	OMNRh$_1$ ♂	OMNRh$_1$ ♀		
42	A$_1$MNRh$_2$	ONRh$_1$	A$_1$MNRh$_1$ ♂	A$_1$MNRh$_1$ ♂			
43	BMRh$_1$	A$_1$MNRh$_1$	OMRh$_1$ ♀	A$_1$BMRh$_1$ ♂			
44	A$_1$MNRh$_1$	OMRh$_1$	OMRh$_1$ ♂	A$_1$MRh$_1$ ♀			
45	A$_1$MRh$_1$	OMRh–	OMRh$_1$ ♂	A$_1$MRh$_1$ ♂			
46	A$_1$MNRh$_2$	BMNRh$_2$	A$_2$NRh– ♀	A$_2$BMRh$_2$ ♂			
47	A$_1$MRh$_1$	A$_2$MNRh$_1$	A$_1$MNRh$_1$ ♂	A$_1$MNRh$_1$ ♂			

* Families 1-7 are the same as families 10, 12, 24, 26, 31, 36, and 37 from the study of Landsteiner and Wiener.

† Child of former marriage.

TABLE III.
Heredity of Subtypes of Rh.

Mating	No. of families	Children of subtype			
		Rh_1	Rh_2	Neg.	Totals
$Rh_1 \times Rh_1$	25	61	4	6	71
$Rh_1 \times Rh_2$	9	19	4	2	25
$Rh_1 \times$ Neg.	9	17	9	1	27
$Rh_2 \times Rh_2$	2	0	3	1	4
$Rh_2 \times$ Neg.	1	0	4	0	4
Neg. $\times$ Neg.	1	0	0	2	2
Totals	47	97	24	12	133

actions than Rh_1 bloods with human antisera (anti-Rh'). Therefore, it may be advisable, when conducting tests with human anti-Rh sera, to include Rh positive controls of subtype Rh_2 as well as Rh_1.

We have studied the heredity of the major subdivisions of the Rh type in 47 families with 135 children (*cf.* Table II). It appears from Table III that the subtypes Rh_1 and Rh_2 resemble the subgroups of A in their hereditary transmission. Thus, it is postulated that there are 3 main allelic genes, Rh_1, Rh_2, and rh, where Rh_1 and Rh_2 are both dominant over rh and Rh_1 is dominant over Rh_2. This theory explains why no children of subtype Rh_1 were encountered in the 4 families with 10 children where neither of the parents belonged to subtype Rh_1. In this connection it may be mentioned that Levine[7] has found that in 17 families with 21 children in which the blood of neither parent was agglutinated by anti-Rh_1 serum, the bloods of all but one of the children failed to react with the serum, and in this single case the possibility of illegitimacy has to be considered.

A further test of the theory is provided by the matings Rh_1 x Rh_1 and Rh_1 x Rh negative. Since Rh_1 individuals must belong to genotype Rh_1Rh_1, Rh_1Rh_2, or Rh_1rh, these families, as is shown in Table II, fall into three groups, depending upon whether the children are all Rh_1, or Rh_1 and Rh_2, or Rh_1 and negative. From the theory it follows that when an Rh_1 parent in these matings has an Rh negative child, none of his children can belong to subtype Rh_2; on the other hand where the Rh_1 parent has given rise to an Rh_2 child, he cannot have Rh negative children. No exception to this rule was encountered in our series of families. A particularly striking case is family No. 20, in which the father is Rh_1 and the mother Rh negative. In this family there are 5 children of subtype Rh_1 and 5 of subtype Rh_2, fulfilling the theoretical expectation under the assumption that the father belongs to genotype Rh_1Rh_2.

Practical application of the heredity of the subtypes of Rh in cases of disputed parentage seems feasible and would afford a slight increase in the chances of exclusion. However, the difficulty in obtaining suitable reagents for the present prevents its general use. Moreover, much more extensive study of families would be necessary to place the theory on a basis safe enough for forensic purposes.

Based on the percentages of the types given in Table 1, the approximate frequencies of the genes are as follows:

$$rh = \sqrt{\text{Neg.}} = \sqrt{0.13} = 36\%$$
$$Rh_2 = \sqrt{\text{Neg.} + Rh_2} - \sqrt{\text{Neg.}} = \sqrt{0.27} - \sqrt{0.13} = 16\%$$
$$Rh_1 = 1 - (Rh_2 + rh) = 48\%$$

It may be noted that the reactions discussed do not exhaust the variety existing among human anti-Rh sera. Thus, recently a serum was encountered which gave strong agglutination with the great majority (but not all) of Rh_2 bloods and only a minority of Rh_1 bloods, while Rh negative bloods failed to react.[8] From a preliminary study, the agglutinogen responsible for the reaction appears to be inherited as a simple Mendelian dominant, probably due to a special allelic gene.

[7] Personal communication.

[8] The properties of this new anti-Rh serum will be presented in detail in a separate report.

Summary. Studies on 47 families with 133 children indicate that the major subtypes Rh_1 and Rh_2 are transmitted by means of corresponding allelic genes Rh_1 and Rh_2 which are both dominant over the gene *rh;* and, in addition, that gene Rh_1 is dominant over Rh_2. (A nomenclature for designating the subdivisions of the Rh positive type is proposed).

14235

The Tocopherol Level in Human Serum During Oral Tocopherol Therapy.*

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In a preceding publication[1] we have described the results of tocopherol studies in human serum by a photoelectric adaptation of the Emmerie and Engel α,α'-bipyridine method.[2] The average tocopherol level for a group of 12 healthy young individuals on an unrestricted diet was 0.96 mg 100 ml of serum. Patients suffering from amyotrophic lateral sclerosis showed slightly lower values within the normal range before tocopherol therapy. The blood level rose after oral administration of the vitamin, but in cases receiving solely intramuscular tocopherol injections a paradoxical drop was noted.

We have now increased the number of cases of amyotrophic lateral sclerosis† and added a group of patients treated orally with tocopherol for myopathies and miscellaneous diseases other than amyotrophic lateral sclerosis.‡ dl-α-Tocopherol acetate in 25 mg tablets was used in all experiments.

The average blood level for 17 untreated cases of amyotrophic lateral sclerosis was 0.67 mg/100 ml and that for 14 miscellaneous myopathies was 0.61 mg/100 ml before treatment. The figures in Tables I and II corroborate the observation that tocopherol ingestion, repeated for several successive days, raises the serum level significantly.

The patients who received treatment are

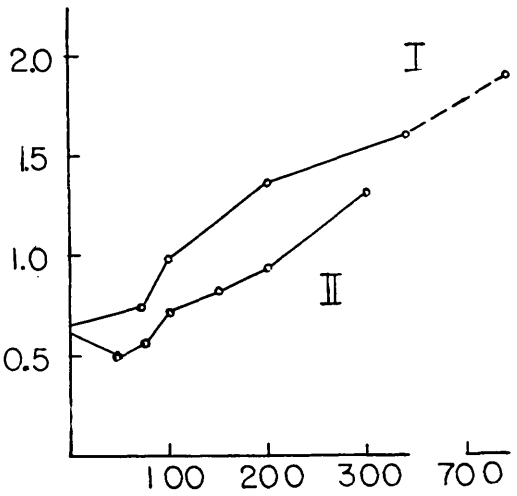

FIG. 1.

Average Serum Tocopherol Level after Administration of Ephynal to Patients with Amyotrophic Lateral Sclerosis (I) and Other Diseases (II).

Ordinates are mg Tocopherol/100 ml serum. Abscissæ are mg Tocopherol administered per day. The points in the graphs represent the average serum tocopherol level for each dosage group. The point given for "0 mg dosage" is the average of all pre-treatment determinations. If the post-treatment level for each dosage group were compared with the pre-treatment level of the corresponding individual group, insignificant changes in the rise of each group would result.

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1 Wechsler, I. S., Gernsheim Mayer, G., and Sobotka, H., PROC. SOC. EXP. BIOL. AND MED., 1941, **47**, 152.

2 Gernsheim Mayer, G., and Sobotka, H., *J. Biol. Chem.*, 1942, **143**, 695.

† A clinical study by I. S. Wechsler, M. R. Sapirstein, and A. Stein of 81 cases, including those studied here, will appear shortly.

‡ We are indebted to the Neurological Service of the Montefiore Hospital for permission to study cases No. 207, 211-213, included in this group.