THE INHERITANCE OF THE MNS BLOOD GROUPS : A SECOND SERIES OF FAMILIES

R. R. RACE, RUTH SANGER, SYLVIA D. LAWLER and DOREEN BERTINSHAW

Medical Research Council, Blood Group Research Unit, Lister Institute, London, S.W. 1

Received 15.ii.49

WHILE examining human sera for Rh antibodies Walsh and Montgomery (1947) found an agglutinin which did not apparently correspond to any of the known blood-group antigens. Sanger and Race (1947) showed that this agglutinin subdivided the three groups of the MN system in such a way that connection between the new antigen, which they called S, and the MN antigens must exist. By statistical analysis of the results of tests on unrelated persons, and by family investigations, they were able to show that the MNS system of blood groups depended either on two pairs of very closely linked genes MS, Ms, NS and Ns, or on four allelomorphs at the MN locus.

A second example of anti-S was soon found (Pickles, 1948), and subsequently several have been recognised ; no example of anti-s has yet been identified, though by analogy with the Rh system there is every reason to anticipate that it will be found.

The MNS blood groups of only 30 families have so far been published (Sanger, Race, Walsh and Montgomery, 1948). The results of testing a further 93 English families for these groups are here presented, and the total of 123 families is examined statistically. The MNS groups of the 93 families are given in table 1. The families were all tested for other blood groups but the addition of these results would confuse the table. Twins are bracketed : when a pair was not shown to be dizygous, by sex or by any of the 6 blood groups for which these families were tested, they have been marked monozygous and scored in the calculations as one child. The high incidence of identical twins in this series of families is due to selection ; 3 of the 4 pairs were sent to us because they were twins thought to be identical.

In table 1 the numbers in the column headed " type of mating " refer to the catalogue of matings given in table 1 of a previous paper (Sanger, Race, Walsh and Montgomery, 1948). In this earlier paper a blood sample which was not agglutinated by the anti-S serum was called for example, MN. As this did not indicate that the blood had been tested with the anti-S serum we now call it MsNs. In the first paper we indicated the phenotype MM anti-S positive, which might be of the genotype MS MS or MS Ms, thus (MM)S ; we have now removed the brackets and have made use of a full stop, thus MM.S.

TABLE 1

The MNS groups of 93 families

No.	Type of mating	Parents		Children					
		Father	Mother	1	2	3	4	5	6
31	2*b*	MSMs	MsMs	MsMs	MSMs	MSMs			
32	2	MM.S	MsMs	MSMs	MSMs				
33	3	MM.S	MM.S	MM.S	MM.S	MM.S			
34	3	MM.S	MM.S	MM.S					
35	3	MM.S	MM.S	MM.S					
36	3	MM.S	MM.S	MM.S	MM.S	MM.S			
37	4*a*	MsMs	MsNs	MsNs	MsNs				
38	4*a*	MsNs	MsMs	MsMs					
39	4*a*	MsNs	MsMs	MsNs					
40	4*a*	MsMs	MsNs	MsMs	MsMs *				
41	4*a*	MsMs	MsNs	MsNs	MsMs	MsNs	MsMs		
42	5*b*	MsNs	MSMs	MSNs	MsMs				
43	5*b*	MSMs	MsNs	MsNs	MSNs	MsMs			
44	5*b*	MsNs	MSMs	MsMs	MSNs	MSMs			
45	5	MM.S	MsNs	MSMs	MSMs	MSNs	MSNs	MSNs	MSNs
46	5	MsNs	MM.S	MSMs	MSMs	MSMs *			
47	5	MM.S	MsNs	MSMs	MSMs				
48	5	MsNs	MM.S	MSMs	MSMs *				
49	5	MsNs	MM.S	MSNs					
50	5	MsNs	MM.S	MSMs	MSMs				
51	6*b*	MsMs	MSNs	MSMs	MsNs	MSMs	MsNs		
52	6*b*	MsMs	MSNs	MSMs	MSMs	MSMs	MSMs		
53	7*e*	MSNs	MSMs	MM.S	MsNs				
54	7*e*	MSNs	MSMs	MM.S	MsNs				
55	7*f*	MsNS	MSMs	MsMs					
56	7	MM.S	MN.S	MM.S	MN.S	MN.S			
57	7	MM.S	MN.S	MM.S	MN.S				
58	7	MM.S	MN.S	MM.S	MM.S				
59	7	MN.S	MM.S	MN.S	MM.S				
60	7	MM.S	MN.S	MN.S					
61	7	MM.S	MN.S	MM.S	MN.S				
62	7	MM.S	MN.S	MN.S	MM.S				
63	7	MN.S	MM.S	MN.S	MM.S				
64	7	MM.S	MN.S	MM.S	MM.S				
65	7	MM.S	MN.S	MM.S	MM.S	MN.S			
66	8*a*	NsNs	MsMs	MsNs	MsNs				
67	8*a*	NsNs	MsMs	MsNs	MsNs	MsNs	MsNs	MsNs	MsNs
68	8*a*	NsNs	MsMs	MsNs	MsNs	MsNs			
69	8*a*	MsMs	NsNs	MsNs					
70	9*b*	MSMs	NsNs	MsNs	MsNs				
71	9*b*	MSMs	NsNs	MSNs	MsNs				
72	9*b*	NsNs	MSMs	MSNs	MsNs	MSNs			
73	9	NsNs	MM.S	MSNs					
74	10	NN.S	MsMs	MsNS					

TABLE 1—*continued*

No.	Type of mating	Parents		Children					
		Father	Mother	1	2	3	4	5	6
75	11*d*	NSNs	MSMs	MsNs	MN.S				
76	11	MM.S	NN.S	MN.S					
77	11	NN.S	MM.S	MN.S	MN.S *				
78	12*a*	MsNs	MsNs	MsNs	MsNs				
79	12*a*	MsNs	MsNs	MsNs	MsMs	NsNs			
80	12*a*	MsNs	MsNs	NsNs					
81	12*a*	MsNs	MsNs	MsNs	NsNs				
82	13*b*	MSNs	MsNs	MSNs	NsNs	MsNs			
83	13*b*	MsNs	MSNs	NsNs	MSNs				
84	13*b*	MsNs	MSNs	MSMs	MSNs	NsNs			
85	13*b*	MSNs	MsNs	NsNs	MSNs	MSMs			
86	13*b*	MsNs	MSNs	MSMs	MsNs	MSNs			
87	13*b*	MSNs	MsNs	NsNs	MSNs	MSNs			
88	13*b*	MSNs	MsNs	NsNs					
89	13*b*	MsNs	MSNs	MSNs	MsNs	MsNs	MSMs	NsNs	
90	13*c*	MsNs	MsNS	MsMs					
91	13 not *a*	MsNs	MN.S	MN.S	MsNs	MN.S			
92	13 not *b*	MsNs	MN.S	NSNs					
93	13 not *c*	MsNs	MN.S	MSMs	MN.S				
94	13	MN.S	MsNs	MN.S					
95	13	MN.S	MsNs	MN.S					
96	14*d*	MSNs	MSNs	NsNs	MSNs				
97	14*d*	MSNs	MSNs	MSMS	MSNs	NsNs	MSMS	MSNs	
98	14*d*	MSNs	MSNs	MSMS	MSMS	NsNs			
99	14*e*	MN.S	MN.S	MN.S	NSNs	MsNs	NSNs		
100	14 not *f*	MN.S	MN.S	MN.S	MM.S				
101	14	MN.S	MN.S	MN.S	MN.S				
102	14	MN.S	MN.S	MN.S	MN.S				
103	15*a*	NsNs	MsNs	NsNs					
104	16*b*	MSNs	NsNs	MSNs	NsNs				
105	16*b*	NsNs	MSNs	MSNs	NsNs				
106	16*b*	NsNs	MSNs	NsNs	NsNs				
107	16*b*	MSNs	NsNs	NsNs					
108	16*b*	NsNs	MSNs	MSNs	NsNs	NsNs			
109	16*c*	MsNS	NsNs	MsNs	MsNs	NSNs			
110	16 not *b*	NsNs	MN.S	NSNs					
111	16 not *b*	MN.S	NsNs	NSNs	NSNs				
112	16 not *c*	NsNs	MN.S	MSNs	MSNs	MSNs			
113	17*d*	NSNs	MSNs	MN.S	NsNs				
114	17	NN.S	MN.S	MN.S	NN.S	MN.S	NN.S		
115	17	MN.S	NN.S	MN.S	MN.S				
116	18*b*	MsNs	NSNs	MsNs	NsNs	NSNs			
117	18	NN.S	MsNs	MsNS					
118	18	NN.S	MsNs	MsNS					
119	19*a*	NsNs	NsNs	NsNs	NsNs	NsNs			
120	21*b*	NsNs	NSNs	NsNs					
121	21*b*	NSNs	NsNs	NSNs	NsNs	NsNs			
122	21*b*	NSNs	NsNs	NsNs					
123	21	NN.S	NsNs	NSNs	NSNs	NSNs			

MN.S written thus indicates that the S gene may be located on either or both the chromosomes. When family grouping makes clear the position of the S, it is written thus, MSNs or MsNS or MSNS.

* = monozygous twins.

The gene frequencies which form the basis of the calculations to follow are those derived by Fisher from the results of tests with anti-M, anti-N and anti-S sera on the red cells of 580 unrelated persons (Walsh and Montgomery, 1947 ; Sanger and Race, 1947 ; Pickles, 1948). They are (Pickles, 1948) :—

MS	0·25585
Ms	0·27863
NS	0·08113
Ns	0·38439

The expected incidence of the 123 families in the 21 phenotypically distinct mating groups can be calculated from these gene frequencies. The expected distribution, and that actually observed, is shown in table 2 ; it will be seen that the agreement between the two sets of figures is close.

TABLE 2

The expected and the observed distribution of the 123 families in the 21 phenotypically distinct mating types

	Mating	Expected		Observed Absolute	χ^2
		Per cent.	Absolute		
1	MsMs × MsMs	0·60	0·74	0	
2	MsMs × MM.S	3·23	3·97	3	
3	MM.S × MM.S	4·33	5·32	6	0·0869
4	MsMs × MsNs	3·33	4·09	7	
5	MM.S × MsNs	8·91	10·96	10	0·0841
6	MsMs × MN.S	4·40	5·41	4	0·3675
7	MM.S × MN.S	11·79	14·50	17	0·4310
8	MsMs × NsNs	2·29	2·82	5	
9	MM.S × NsNs	6·15	7·56	6	0·3219
10	MsMs × NN.S	1·07	1·32	1	
11	MM.S × NN.S	2·87	3·53	6	
12	MsNs × MsNs	4·59	5·65	7	0·3226
13	MN.S × MsNs	12·14	14·93	15	0·0003
14	MN.S × MN.S	8·03	9·88	12	0·4549
15	MsNs × NsNs	6·33	7·79	2	4·3035
16	MN.S × NsNs	8·38	10·31	10	0·0093
17	MN.S × NN.S	3·91	4·81	3	
18	MsNs × NN.S	2·95	3·63	4	
19	NsNs × NsNs	2·18	2·68	1	
20	NN.S × NN.S	0·48	0·59	0	
21	NN.S × NsNs	2·04	2·51	4	
		100·00	123·00	123	
Sum of 11 smaller classes . . .			30·69	34	0·3570
χ^2 for 10 degrees of freedom =					6·7390

Probability between 0·8 and 0·7.

In the first place we propose to confine our analysis to the S gene and its allelomorph s. At present s cannot be recognised in a positive

way for no anti-s serum has yet been found. The position of the gene s is that which was, until recently, held by the Rh genes e and d, and the antigen s may be considered for the time being as a recessive character only recognisable as an absence of S. We cannot say whether a person belongs to the group SS or Ss without the knowledge of the groups of other members of his family, for both types of red cell are agglutinated by the anti-S serum, and so far we have not observed any clear dosage effect which would distinguish the two types of blood.

From the gene frequencies given above we may, by addition, obtain the following frequencies for S and s.

$$S = 0{\cdot}33698$$
$$s = 0{\cdot}66302$$

and the frequencies of the three genotypes will be

$$SS = 0{\cdot}11356$$
$$Ss = 0{\cdot}44685$$
$$ss = 0{\cdot}43960$$

From these may be derived the expected frequencies of the various types of mating and of the issue expected therefrom. These are given in table 3.

TABLE 3

The expected frequencies of the various types of S mating and the issue expected therefrom

Mating		Children		
Type	Frequency	SS	Ss	ss
SS × SS . . .	0·0129	0·0129	...	...
SS × Ss . . .	0·1015	0·05075	0·05075	...
Ss × Ss . . .	0·1997	0·04992	0·09985	0·04992
SS × ss . . .	0·0999	...	0·0999	...
Ss × ss . . .	0·3929	...	0·19645	0·19645
ss × ss . . .	0·1932	...	...	0·1932
	1·0001	0·11357	0·44695	0·43957

The figures in table 3 have been used to calculate the expected incidence in the three phenotypically distinguishable mating types of the 123 pairs of parents, together with the expected distribution of the S groups in their 293 children. These expectations are given in table 4, where they are compared with the observed numbers ; once again the agreement is close.

Such an analysis shows that the S antigen is inherited as a dominant character, it does not disclose the very close relationship between the Ss genes and the MN genes.

Sanger and Race (1947) demonstrated that the antigen S depended on a gene S, with presumably, an allelomorph s, and that these genes were either part of the MN genes or, more probably, very closely linked to the MN genes. The linkage is so close that no crossing over

TABLE 4

The S groups of 123 families with 293 children

Mating			Children					
Type	Number		Number	S		ss		χ^2 for 1 d.f.
	Expected	Observed		Expected	Observed	Expected	Observed	
S×S	38·6	*44*	104	87·5	*92*	16·5	*12*	1·46
S×ss	60·6	*57*	136	81·8	*84*	54·2	*52*	0·15
ss×ss	23·8	*22*	53	0·0	*0*	53·0	*53*	...
	123·0	*123*	293					

has been observed in those of the 123 families capable of disclosing it : that is families of at least 2 children, shown by one of the children to be of the mating types 6*b* or *c*, 7*e* or *f*, 13*b* or *c*, 14*d*, *e* or *f*, 16*b* or *c* or 17*d* or *f*. The children in these relevant families number 82. Nor was crossing over expected in such a small sample, for if crossing over occurs at all freely the ratio of MS : Ms genes would be expected to equal that of NS : Ns which is not the case. The situation is very like that found in the Rh system, and will be exactly so when an anti-s antibody is found ; such an antibody will agglutinate the blood of about 89 per cent. of Englishmen.

A more complex analysis of the 123 families is given in table 5 which shows the expected and the observed incidence of the 293 children in the 6 phenotype groups. Taking into account the small numbers of children from some of the mating types there is seen to be good agreement between the observed and expected numbers.

It will be seen from table 2 that 19 of the possible 21 phenotypically different matings are represented. The 123 families demonstrate unequivocally 21 of the 55 genotypically different matings shown in table 1 of the earlier paper.

Family No. 89 (fig. 1) may be taken as an example of the effect of the anti-S serum on the MN blood groups. Without the information given by the anti-S serum it could only have been said that child 4 had received a paternal and maternal M gene, and child 5 a paternal and maternal N gene. The origin of each of the genes of the first 3 children was ambiguous, it might have been paternal or maternal. The anti-S serum, however, makes clear the origin of all the genes of these three children.

The anti-S serum will contribute greatly to the usefulness of the MN blood groups as markers for linkage owing to the increased number of recognisable heterozygotes.

TABLE 5

Showing the expected and the observed incidence of children in the 6 phenotype groups

	Mating	Total	Children											
			MsMs		MM.S		MsNs		MN.S		NsNs		NN.S	
			Exp.	Ob.	Exp.	Ob.	Exp.	Ob.	Exp.	Ob.	Exp.	Ob.	Exp.	Ob.
1	MsMs × MsMs	0	0·00	0	...	...	...	...	...	...	...	...	...	...
2	MsMs × MM.S	8	2·74	1	5·26	7	...	...	...	...	...	...	...	...
3	MM.S × MM.S	15	1·76	0	13·24	15	...	...	...	...	...	...	...	...
4	MsMs × MsNs	16	8·00	7	...	...	8·00	9	...	...	...	...	...	...
5	MM.S × MsNs	25	4·28	3	8·22	11	4·28	1	8·22	10	...	...	...	. .
6	MsMs × MN.S	19	1·52	0	7·98	10	6·59	9	2·91	0	...	...	...	...
7	MM.S × MN.S	34	0·93	1	16·07	21	4·04	3	12·96	9	...	...	...	...
8	MsMs × NsNs	13	...	...	...	...	13·00	13	...	...	...	...	...	...
9	MM.S × NsNs	12	...	...	...	...	4·11	6	7·89	6	...	...	...	...
10	MsMs × NN.S	1	...	...	...	...	0·45	0	0·55	1	...	...	...	...
11	MM.S × NN.S	14	...	...	...	...	2·17	2	11·83	12	...	...	...	...
12	MsNs × MsNs	16	4·00	2	...	...	8·00	11	...	...	4·00	3	...	...
13	MN.S × MsNs	35	1·40	1	7·35	5	7·47	6	10·03	15	6·07	7	2·68	1
14	MN.S × MN.S	33	0·21	0	8·04	8	1·82	2	14·67	16	3·97	3	4·27	4
15	MsNs × NsNs	5	...	...	...	...	2·50	2	...	...	2·50	3	...	...
16	MN.S × NsNs	22	...	...	...	...	1·76	4	9·24	6	7·63	7	3·37	5
17	MN.S × NN.S	8	...	...	...	...	0·29	0	3·71	5	1·26	1	2·74	2
18	MsNs × NN.S	6	...	...	...	...	1·36	2	1·64	2	1·36	1	1·64	1
19	NsNs × NsNs	3	...	...	...	...	...	...	...	...	3·00	3	...	...
20	NN.S × NN.S	0	...	...	...	...	...	...	...	...	0·00	0	0·00	0
21	NN.S × NsNs	8	...	...	...	...	...	...	...	...	3·62	4	4·38	4
		293	24·84	15	66·16	77	65·84	70	83·65	82	33·41	32	19·08	17

Total expected 292·98 Total observed 293

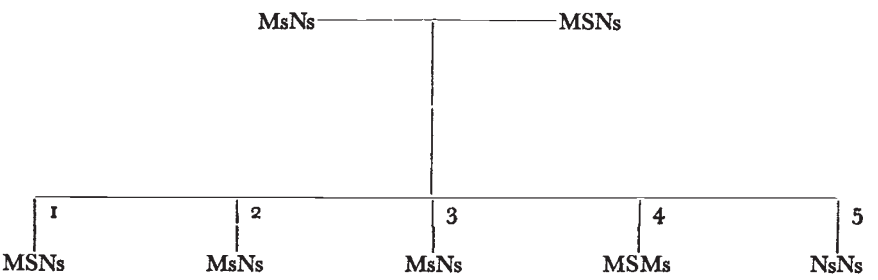

FIG. 1.—Family number 89.

Professor Fisher has pointed out that the MNS system is now more efficient in making distinction between two human beings than the A_1 A_2 B O system and only slightly less so than the Rh system. This

efficiency may be compared as follows : the sums of the squares of the phenotype frequencies represent the percentage of failures to distinguish between two random samples of English blood ; they are :—

$A_1 A_2$ B O	.	32·8	per cent.	failures,	or	67·2	per cent.	efficient
MNS . .	.	20·2	,,	,,	,,	79·8	,,	,, ,,
Rh . .	.	19·5	,,	,,	,,	80·5	,,	,, ,,

The proportion of failures to recognise (*a*) erronious parentage, or (*b*) erronious paternity, the mother being known, is of course larger, but the relation value of the three factors is much the same.

When the anti-s serum becomes available the MNS will be much the most useful, genetically, of all the systems so far known. The $A_1 A_2$ B O calculations are based on the observed phenotype frequencies in 3459 samples tested with anti-A, anti-B and a_1, by Ikin, Prior, Race and Taylor (1939). The MNS calculations are based on the observed phenotype frequencies in the collected figures of the first three groups of workers given in table 6. The Rh calculations are based on the observed frequencies of the phenotypes in 1073 samples of blood tested with anti-D, -C, -c, -C^w, -E and -e (Race, Mourant, Sanger and Lawler, 1948).

TABLE 6

The frequency of the 6 phenotypes of the MNS system

	MM.S	MsMs	MN.S	MsNs	NN.S	NsNs	Total
Walsh and Montgomery .	30	9	40	27	13	21	**140**
Sanger and Race . .	36	14	57	38	15	30	**190**
Pickles	55	20	67	63	12	33	**250**
Present series . . .	74	23	104	78	29	56	**364**
	195	66	268	206	69	140	**944**
	0·2066	0·0699	0·2839	0·2182	0·0731	0·1483	1·0000
	261		474		209		944
	0·2765		0·5021		0·2214		1·0000

Since the publication of our original tests on 190 unrelated persons we have tested a further 364 samples (including most of the parents of the families here described). The results are given in table 6 together with the figures previously published. The 364 were not available when Fisher calculated the gene frequencies which we have used in this paper ; their inclusion would not make any material difference to the results.

SUMMARY

The MNS groups of 93 English families have been determined. The results, combined with those previously published for 30 families, have been examined statistically, and are consistent with the hypothesis that S and s are genes very closely linked to the MN genes. So far

no recombination has been observed among 82 relevant children. The results are given of testing a further series of 364 unrelated English persons for these groups.

Acknowledgments.—We are most grateful to Dr M. M. Pickles of the Pathological Department, Radcliffe Infirmary, Oxford, who discovered the second example of anti-S serum and gave us a most generous supply.

We also wish to thank the members of the families for allowing us to take samples of their blood.

REFERENCES

IKIN, ELIZABETH W., PRIOR, AILEEN M., RACE, R. R., AND TAYLOR, G. L. 1939.
The distributions in the A_1 A_2 B O blood groups in England.
Ann. Eugen., Lond., *9*, 409.

PICKLES, MARGARET M. 1948.
A further example of the anti-S agglutinin.
Nature, *162*, 66.

RACE, R. R., MOURANT, A. E., LAWLER, SYLVIA D., AND SANGER, RUTH. 1948.
The Rh chromosome frequencies in England.
Blood, *3*, 689.

SANGER, RUTH, AND RACE, R. R. 1947.
Subdivisions of the MN blood groups in man.
Nature, *160*, 505.

SANGER, RUTH, RACE, R. R., WALSH, R. J., AND MONTGOMERY, CARMEL. 1948.
An antibody which subdivides the human MN blood groups.
Heredity, *2*, 131.

WALSH, R. J., AND MONTGOMERY, CARMEL. 1947.
A new human iso-agglutinin subdividing the MN blood groups.
Nature, *160*, 504.