Absence of Linkage Between the Genes Responsible for the Sickling Phenomenon, the MN Blood Types, and the S-agglutinogen[1]

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SNYDER, RUSSEL, AND GRAHAM (1947) and Snyder, Clarke, and Moore (1949) have reported autosomal linkage in the American Negro between the genes responsible for the sickling phenomenon and the MN blood types. Sanger and Race (1947), Sanger, Race, Walsh and Montgomery (1948) and Race, Sanger, Lawler, and Bertinshaw (1949) have established the existence of a human ag-

TABLE 1. METHOD OF DESIGNATING THE GENOTYPES:

	Normal *sksk*	Sickle cell trait *Sksk*	Sickle cell disease *SkSk*
MM	a_{11}	a_{12}	a_{13}
MN	a_{21}	a_{22}	a_{23}
NN	a_{31}	a_{32}	a_{33}

a. Where *M* and *N* represent the genes responsible for the respective blood antigens, and *sk* and *Sk* represent the genes responsible for normal red blood cells and those exhibiting the sickling phenomenon.

	S-negative *ss*	S-positive *Ss* or *SS*
Normal *sksk*	b_{11}	b_{12}
Trait *Sksk*	b_{21}	b_{22}
Disease *SkSk*	b_{31}	b_{32}

b. Where *S* represents the gene responsible for the S-reaction and *s* its recessive allele, and *Sk* and *sk* have the same significance as above.

glutinogen termed S, which is non-randomly associated with the MN blood types, the relationship permitting of two explanations: (1) there are four alleles, *MS*, *M*, *NS*, and *N*, or (2) there is a pair of alleles, *S* and *s*, closely linked to the genes responsible for the MN blood types, no recombination having

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TABLE 2. TEST OF LINKAGE BETWEEN THE GENES RESPONSIBLE FOR THE SICKLING PHENOMENON AND THE MN BLOOD TYPES, IN FAMILIES WHERE BOTH PARENTS WERE STUDIED

MATING NUMBER	FINNEY MATING TYPE	a_{11}	a_{12}	a_{13}	a_{21}	a_{22}	a_{23}	a_{31}	a_{32}	a_{33}	a	b	c	d	s	SCORE	VARIANCE
2	20							1	1		1		1		2	−1	1
6	21	1	1				1					1	1		2	1	1
19	21				1				2			2			2	1	1
22	21				1	1	1	2			1	1	2		4	0	6
39	21				1	2				1	1			1	2	1	1
48	21				1	1	1				1	1			2	−1	1
53	21						2					2			2	1	1
57	21					2	2			1		2		1	3	−1	3
64	21				1	2	1		2		1	1			2	−1	1
79	21		3		1			1	1		3	1		1	5	2	10
81	21	1		1		1	1					1	1	1	3	−1	3
90	21				2	1					2				2	1	1
91	21				1	2	2				1	2			3	−1	3
93	21						2	1	1	1		2	1	1	4	0	6
98	20				1	1		1	1		1	1	1	1	4	−2	6
99	20				3	1		3				1	3	3	7	−3	21
110	21						2					2			2	1	1
111	21	1	2		3	3		1	3		2	3	1	1	7	−3	21
113	22			1		1				1			1	1	2	−2	4
118	20	3	1		1						1		3	1	5	−2	10
20-S	21	1	1	1									1	1	2	−1	1
26-S	20				1				1		1			1	2	1	1
31-S	20					1			2		2	1			3	−1	3
32-S	20		1			1					1	1			2	−1	1
Total															74	−12	108

TABLE 3. TEST OF LINKAGE BETWEEN THE GENES RESPONSIBLE FOR THE SICKLING PHENOMENON AND THE MN BLOOD TYPES, IN FAMILIES WHERE ONLY ONE PARENT WAS TESTED AND WAS HETEROZYGOUS FOR BOTH FACTORS

MATING NUMBER	a_{11}	a_{12}	a_{13}	a_{21}	a_{22}	a_{23}	a_{31}	a_{32}	a_{33}	A_1	A_2	A_3	P_1	P_2	P_3	A	k
2-S							1	1			−1	−1		.3333	.6667	−1.000	1.000
8-S	1	2	1	2						−1	−2		.8889	.1111		−1.111	13.111
11-S	1	1		1	1					−2	−1		.6667	.3333		−1.667	3.222
22-S				1	2	2				−2	0	−2	.2500	.5000	.2500	−1.000	2.500
23-S	1			1			1	1			−1			1		−1.000	3.000
28-S		2								1	1		.6667	.3333		1.000	1.000
100			1	1	1					1	0		.5000	.5000		.500	.750
29	1			1	1		2	1			−2			1		−2.000	6.000
30					1	1	1				0	−1		.5000	.5000	−.500	.750
31				3	3		1				−3	0		.5000	.5000	−1.500	5.250
36					2					1	0	1	.2500	.5000	.2500	.500	.250
44				1			1	1	1		−2	−1		.2000	.8000	−1.200	4.920
46	1		1		3					6	−2		.6667	.3333		3.000	5.000
Total																−5.978	46.753

been observed among 82 relevant children. If the latter interpretation is correct, then from the studies of these two groups of investigators emerges the possibility of an autosomal linkage group in man composed of three genes with clear cut effects.

Recent investigations in this laboratory have established the fact that the sickling phenomenon of the erythrocytes of the American Negro is due to a gene (*Sk*) which in heterozygotes produces the apparently harmless sickle cell trait and in homozygotes the more serious sickle cell disease (Neel, 1949, 1951). The exact genetic relationship between the sickle cell trait and sickle cell disease was not known to Snyder et al at the time of their studies, and both trait and disease were considered to be variable manifestations of the same dominant gene.

TABLE 4. TEST OF LINKAGE BETWEEN THE GENES RESPONSIBLE FOR THE SICKLING PHENOMENON AND THE S-REACTION, IN FAMILIES WHERE BOTH PARENTS WERE TESTED

MATING NUMBER	FINNEY MATING TYPE	b_{11}	b_{12}	b_{21}	b_{22}	b_{31}	b_{32}	a	b	c	d	s	SCORE	VARIANCE
6	4		1		1	1		1			1	2	1	1
22	4	2	1		1		1	1	1	2		4	0	6
39	4		1		2	1		1			1	2	1	1
48	4	1		1		1				1	1	2	−1	1
57	4			2		3					3	3	3	3
79	3	2		1	3				3	2	1	6	5	15
40	4					1	1		1		1	2	−1	1
55	4	1	1	4			2	1	2	1		4	0	6
59	3	2	2	1	2			2	2	2	1	7	−3	21
65	4		1	2			2	1	2			3	−1	3
Total												35	4	58

In connection with our studies on the genetics of the sickling phenomenon in the American Negro, we have had occasion to accumulate additional data bearing on the question of linkage between the *Sk* and *MN* and *S* genes. Through the kindness of Dr. R. R. Race we have had available for our use a limited quantity of anti-S serum. That portion of our data bearing on the relation between the M-N and S reactions in American Negros has already been presented (Neel and Hanig, 1951). In corroboration of the findings of others, the two alternative possible relationships mentioned above between *M-N* and *S* were confirmed, no recombination being observed in 18 relevant children. The present paper will analyze the linkage relationships of the *Sk* gene to the *M-N* and *S* genes. In the analysis, the M-N and S reactions will be treated as if determined by separate albeit closely linked genes.

Material. The findings in those of the families in our series which yield in-

formation relevant to the question of linkage are summarized in tables 2, 3, and 4. The children in these families have been scored as to the information they yield concerning linkage according to the method proposed by Finney (1940, 1941). Table 1 presents the code designations used to describe the children. From these code designations plus a knowledge of the Finney mating types, the exact composition of any family can be reconstituted.

Discussion and Conclusions. The present data provide no evidence for a linkage between the *Sk* gene and those responsible for either the M-N or S reactions, the *u*-scores for *Sk* and *MN* being negative (tables 2 and 3), and for *Sk* and *S* positive but well below the level of significance (table 4).

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