A Genetic Study of the Antigens Associated with the Gm(b) Factor of Human Gamma Globulin

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SEVERAL ALLELES at each of two independent loci determine hereditary factors in human gamma globulin (review in Steinberg, 1962b). The alleles at one locus, *Gm*, determine hereditary factors in the heavy (H) chain of 7S gamma globulin (synonyms γ_2, $7S\gamma_{ss}$). (See Lawler in Cohen, 1963; Polmar and Steinberg, 1964.) One of these factors, Gm(b), may be determined by any one of at least four different alleles. In Caucasoids, it is determined by the allele Gm^b; in Negroids by either a Gm^{ab} or a Gm^{abc} allele, and by a different Gm^{ab} allele in all other races tested to date (Harboe, 1959; Steinberg, Stauffer, and Boyer, 1960; Steinberg and Wilson, 1963a). Evidence has been accumulating since 1961 that each of these alleles determines a Gm(b) factor which is composed of a series of antigens (see Ropartz, Rivat, and Rousseau, 1963, for review).

Ropartz, Rivat, and Rousseau (1963) demonstrated that seven antisera which gave concordant results for Gm(b) in whites gave three different patterns of reactions in Japanese. For convenience they called these patterns Gm(bα), Gm(bβ) and Gm(bγ). These patterns, however, were not the same for isolated individuals of other races. Indeed two French individuals also showed discordances in that they were Gm(b+) with some of the antibodies and Gm(b−) with others. Ropartz and his colleagues had no families to study; hence they could offer no genetic hypothesis to explain their results. A similar demonstration of different Gm(b) factors in whites was presented in data for an English family studied in this laboratory (Steinberg, Stauffer, and Dunsford, 1963).

These observations raised the question of what relation the different Gm(b) antigens bear to the known alleles which produce the Gm(b) factors and whether these antigens define new alleles.

This communication is a report of population and family studies with four anti-Gm(b) antisera. The studies were done to obtain answers to the above questions.

MATERIALS AND METHODS

The Samples

The serum samples were (a) a panel of 100 sera from white donors; (b)

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TABLE 1. REAGENTS USED AS STANDARDS TO DETERMINE THE GM FACTORS OF γ-GLOBULIN

Factor	Anti-γ-globulin		Anti-D	Dilution*
	Antibody	Dilution		
Gm(a)	Wils	1/8	251	1/5
Gm(b)	Bomb	1/32	E. W.	1/3
	Draves	1/4	E. W.	1/3
Gm(x)	Taylor	1/32	Ham	1/5
Gm(c)	Carp	1/32	Warren	1/5
	Kellum	1/8	Warren	1/5
Gm(b^w)	Da	1/4	Roehm	1/5

*The tested serum was diluted 1/16 for all initial tests. Sera giving unusual results were tested at two-fold serial dilutions from 1/2 through 1/64. Many of the samples were tested several times.

a panel of 105 sera from American Negro donors; (c) sera from several hundred Brazilian families of mixed white, Negro, and South American Indian ancestry (Morton, 1964); population samples of (d) Japanese, (e) Chinese, (f) North American Indians, (g) Eskimos, (h) African Negroes, (i) Australian aborigines, and (j) Melanesians from New Guinea.

Typing

The determination of the γ-globulin factors was done as previously described (Steinberg, 1962b). All the samples were initially typed (for other purposes) with the standard reagents listed in Table 1 for Gm(a), Gm(b), Gm(x), Gm(c), and Gm(b^w). They were subsequently typed with antibodies Th and Bu. Antibody Th was diluted 1/4 and Bu was diluted 1/8. Both were used with anti-D E. W. diluted 1/3. Antibodies Th and Bu are from healthy nonrheumatoid donors, the former from a Negro woman, the latter from a white woman.

DATA

The White Panel

Sixty-seven of the 100 sera in the white panel were Gm(b+) when tested with our standard anti-Gm(b) reagents, Bomb and Draves. All 67 were positive with antibodies Da, Th, and Bu. None of the 33 Gm(b−) sera were positive with Da, Th, or Bu. We conclude that in whites Da, Th, and Bu test for Gm(b).

The American Negro Panel

The data for the 105 samples in this panel are presented in Table 2. The symbol "b^w" refers to those samples which are positive with the antiserum Da (Steinberg and Wilson, 1963a). The seven samples which were Gm(b−) (lines 1 and 2, Table 2) were negative with antisera Da and Bu, but two individuals whose phenotype was Gm(a) (line 1, Table 2) were positive with Th. All 25 Gm(b^w+) samples (last four lines of Table 2) were Th and Bu positive as well. It has been shown (Steinberg and Wilson, 1963a) that in

TABLE 2. REACTIONS OF 105 SERUM SAMPLES FROM AMERICAN NEGROES, OF KNOWN GM PHENOTYPE, WITH ANTIBODIES TH AND BU

Gm Phenotype*	No.	Th(+) Bu(+)	Th(+) Bu(−)	Th(−) Bu(+)	Th(−) Bu(−)	Th(+) No.	Th(+) %	Bu(+) No.	Bu(+) %
1. a†	6	0	2	0	4	2	33	0	0
2. ax	1	0	0	0	1	0	..	0	..
3. ab	32	32	0	0	0	32	100	32	100
4. abx	2	0	0	2	0	0	..	2	100
5. abc	36	26	2	0	8	28	78	26	72
6. abxc	3	0	0	0	3	0	..	0	..
7. abb^w	11	11	0	0	0	11	100	11	100
8. abxb^w	1	1	0	0	0	1	100	1	100
9. abcb^w	8	8	0	0	0	8	100	8	100
10. bb^w	5	5	0	0	0	5	100	5	100

*All individuals were tested with the standard reagents listed in Table 1 for Gm(a), Gm(b), Gm(x), Gm(c), and Gm(b^w), but only the positive reactions are recorded.

†The generic name of the locus *(Gm)* is omitted.

American Negroes b^w(+) is due to the presence of the Gm^b allele from white ancestry. Hence, the reactions of these 25 sera with Th and Bu are in accordance with the data from the white panel.

Further disagreements among the reactions with antibodies Draves, Da, Th, and Bu occur among individuals who are Gm(b+) and Gm(b^w−) (lines 3–6, Table 2). While all 73 of these individuals are positive when tested with Draves [necessarily so because this antiserum defines Gm(b)] and negative with Da [recall that Da defines Gm(b^w)], both the Gm(a+b+x+) individuals (line 4, Table 2) are Th(−), Bu(+), and two of the 36 Gm(a+b+c+) individuals (line 5, Table 2) are Th(+), Bu(−). All other individuals in this group (lines 3–6, Table 2) are either Th(+), Bu(+), (58/73), or Th(−), Bu(−), (11/73). Hence, among Draves(+), Da(−) individuals all four possible combinations of reactions with Th and Bu have occurred. It is of interest to note for future reference that the three Gm(a+b+c+x+) individuals (line 6, Table 2) were (Th−Bu−). The genotype of such individuals is Gm^{ax}/Gm^{abc}. Note that while in the white panel only two of the four possible patterns of reactions to Th and Bu were observed [namely, Th(−), Bu(−) and Th(+), Bu(+)], all four were observed in the Negro panel.

While these data establish that antisera Th and Bu are not identical with Draves or Da, they are not adequate for the characterization of these antibodies.

Family Data

Serum samples from 214 of 1056 Brazilian families of mixed white, Negro, and Indian ancestry collected by Dr. Newton Morton (Morton, 1964) were used for this study. Of the 214 families, 133 were studied in sequence without selection; the remainder were selected to test a hypothesis developed from the data for the first set of families (see below). In 113 of the 133 families studied without selection, the tests with Th and Bu always agreed with each other but not necessarily with Da. Tests with Th and Bu were always positive when the test with Da was positive, but both were sometimes positive when the test with Da was negative. The data are too extensive to publish in detail,

TABLE 3. DATA FROM FAMILIES ILLUSTRATING CONCORDANCE BETWEEN THE REACTIONS WITH ANTISERA TH AND BU AND DISCORDANCE BETWEEN THESE AND ANTISERUM DA

See text for further explanation.

Family		Phenotype*†	Da	Th	Bu	Probable genotype*
132	Fa	abx	−	+	+	*ax/ab*
	Mo	ab	+	+	+	*a/b*
	1‡	ab	+	+	+	*ab/b*
	1	ab	−	+	+	*a/ab*
	2	abx	+	+	+	*ax/b*
	1	ax	−	−	−	*a/ax*
48	Fa	ab	−	+	+	*a/ab* or *ab/ab*
	Mo	ab	+	+	+	*a/b* or *ab/b*
	4	ab	+	+	+	*a/b* or *ab/b*
	2	ab	−	+	+	*a/ab* or *ab/ab*
112	Fa	abx	−	+	+	*ax/ab*
	Mo	ab	+	+	+	*a/b*
	3	ab	−	+	+	*a/ab*
	2	abx	+	+	+	*ax/b*
	2	ax	−	−	−	*a/ax*
	1	ab	+	+	+	*ab/b*
133‖	Fa	abc	+	+	+	*abc/b*
	Mo	abc	+	+	+	*abc/b*
	3	abc	+	+	+	*abc/b*
	1	abc	−	−	−	*abc/abc*
	1	b	+	+	+	*b/b*

*The generic name of the locus (*Gm*) is omitted.

†The phenotypes were determined with the standard reagents listed in Table 1.

‡This number indicates how many offspring had the listed phenotype.

‖This family is included to demonstrate the reactions of a Gm^{abc}/Gm^{abc} homozygote with antibodies Da, Th, and Bu.

but data from some illustrative families are presented in Table 3. In each of the remaining twenty families, at least one member showed a discrepancy between the reactions with Th and Bu reagents. Data from two illustrative families along with their probable genotypes are presented in Table 4. The data for the remaining 18 families may be found in the appendix. The probable genotypes are not supplied for these families because in most cases there is uncertainty about one allele among the parents and among some of the children. Thus, in family 4 the father's genotype is probably Gm^{ab}/Gm^{ab}, but the offspring do not prove this; in family 14, the father's genotype may be, as far as the family data are concerned, Gm^{a}/Gm^{b}, Gm^{a}/Gm^{ab}, Gm^{b}/Gm^{ab}, or Gm^{ab}/Gm^{ab}. Our tests with Da, Th and Bu lead us to conclude his genotype is Gm^{b}/Gm^{a} or Gm^{b}/Gm^{ab}.

The reader will see from these few examples that it is virtually impossible to summarize the data in a brief and meaningful manner. The patterns are equally as varied for the 120 families in which the tests with Th and Bu were concordant and therefore the detailed data for them are omitted.

TABLE 4. DATA FROM FAMILIES ILLUSTRATING DISCORDANCE BETWEEN THE REACTIONS WITH ANTISERA TH AND BU
See text for further explanation.

Family		Phenotype*†	Da	Th	Bu	Genotype*
108	Fa	ab	+	+	+	*a/b*
	Mo	ax	−	−	−	*a/ax*
	2‡	ab	+	+	+	*a/b*
	1	a	−	+	−	*a/a*
	1	ax	−	+	−	*a/ax*
	1	abx	+	+	+	*ax/b*
29	Fa	ab	−	+	+	*a/ab*
	Mo	ab	−	−	+	*a/ab*
	4	ab	−	+	+	*a/ab* or *ab/ab*
	2	a	−	−	−	*a/a*

*The generic name of the locus *(Gm)* is omitted.
†The phenotypes were determined with the standard reagents listed in Table 1.
‡This number indicates how many offspring had the listed phenotype.

Families number 132, 48, and 112 (Table 3) demonstrate the presence of Gm^{ab} alleles negative for the antigen(s) detected by Da but positive for those detected by Th and Bu. Families 132 and 112 illustrate also the presence of Gm^{a} and Gm^{ax} alleles negative for the antigens detected by these three antisera. Family 133 demonstrates that the Gm^{abc} allele is negative for the antigens detected by antibodies Da, Th, and Bu. We recognize that these arguments are based on probable genotypes, but the genotypes seem reasonable and offer sufficient grounds to form a working hypothesis (see below).

The data in Table 4 illustrate the presence of a Gm^{a} allele positive for the antigen(s) detected by Th (family 108) and of a Gm^{ab} allele negative for this antigen(s) (mother of family 29).

The data from the families in Tables 3 and 4 and from similar families in this series of 133 families led us to postulate (1) that the antibody Bu detects an antigen produced by the Gm^{b} and Gm^{ab} alleles but not by the Gm^{abc}, Gm^{a}, or Gm^{ax} alleles and (2) that the antibody Th detects an antigen produced by the Gm^{b} allele, by some Gm^{ab} alleles but not others, by some Gm^{a} alleles but not others, but not by the Gm^{abc} or the Gm^{ax} alleles. (See Table 8, which will be referred to again later.)

Another 81 Brazilian families, whose phenotypes, as noted above, had been determined for Gm(a), Gm(b), Gm(x), Gm(c), and Gm(b^w), were selected for tests with Th and Bu because they offered the possibility of testing the hypothesis advanced above. The data from these families agreed with the hypothesis.

The data gathered from the 1,341 individuals in the 214 families are summarized in Table 5. Genotypes recorded as definite have been determined by family data; those listed with alternative possibilities were not definitely clarified by family data. All 728 sera listed as coming from donors with at least one Gm^{b} allele (lines 14–19, Table 5) were Gm(b^w+), confirming our earlier observations (Steinberg and Wilson, 1963a) that the Gm^{b} allele de-

TABLE 5. REACTIONS WITH ANTISERA TH AND BU OF SERUM SAMPLES FROM PARENTS AND OFFSPRING FROM 214 BRAZILIAN FAMILIES OF MIXED WHITE, NEGRO, AND SOUTH AMERICAN INDIAN ANCESTRY

Genotype*†	No.	Th(+) Bu(+)	Th(+) Bu(−)	Th(−) Bu(+)	Th(−) Bu(−)	Th(+)		Bu(+)	
						No.	%	No.	%
1. *a/a*	91	0	30	0	61	30	33	0	—
2. *a/ax*	78	0	13	0	65	13	17	0	—
3. *a* or *ax/ax*	4	0	0	0	4	0	—	0	—
4. *ax/ax*	3	0	0	0	3	0	—	0	—
5. *a/ab*	95	83	0	12	0	83	87	95	100
6. *ax/ab*	60	50	0	10	0	50	83	60	100
7. *a* or *ab/ab*	125	120	0	5	0	120	96	125	100
8. *ab/ab*	2	2	0	0	0	2	100	2	100
9. *a/abc*	23	0	3	0	20	3	13	0	—
10. *ax/abc*	27	0	0	0	27	0	—	0	—
11. *a* or *ab/abc*	92	56	4	3	29	60	65	59	64
12. *ab/abc*	12	12	0	0	0	12	100	12	100
13. *abc/abc*	1	0	0	0	1	0	—	0	—
14. *a/b*	114	114	0	0	0	114	100	114	100
15. *ax/b*	97	97	0	0	0	97	100	97	100
16. *a* or *ab/b*	256	256	0	0	0	256	100	256	100
17. *ab/b*	43	43	0	0	0	43	100	43	100
18. *abc/b*	67	67	0	0	0	67	100	67	100
19. *b/b*	151	151	0	0	0	151	100	151	100
Totals	1341	1051	50	29	211	1101	82.1	1080	80.5

*The generic name of the locus *(Gm)* is omitted.

†The phenotypes were determined with the standard reagents listed in Table 1; the genotypes corresponding to these phenotypes were determined from family data.

termines the Gm(b^w) antigen(s) also. In agreement with our panel studies, these 728 sera were positive for the antigens detected by Th and Bu. Hence, the Gm^b allele determines the antigens detected by antisera Draves, Da, Th, and Bu.

Thirty-one samples came from donors who had only Gm^{ax}, or Gm^{abc} alleles, or both (lines 4, 10 and 13, Table 5). All 31 were negative for the antigens detected by antisera Da (not shown in the table), Th, and Bu. Among the Gm(a) homozygotes, 33% were positive with Th (line 1, Table 5); hence, the frequency of Gm^a alleles negative with Th = $\sqrt{.67} = .82$, and those positive with Th = $1 - .82 = .18$. We would expect therefore that 18% of the Gm^a/Gm^{ax} (line 2, Table 5) and of the Gm^a/Gm^{abc} (line 9, Table 5) individuals would be Th(+), since the Gm^{ax} and Gm^{abc} alleles are negative for Th. The observed frequencies are 17% and 13%, respectively (Table 5.). Neither differs significantly from the expected 18%.

Of the 60 Gm^{ax}/Gm^{ab} individuals (line 6, Table 5), 17% were Th(−); all were Bu(+). We could expect 17%, that is, two of the 12 Gm^{ab}/Gm^{abc} individuals (line 12, Table 5) to be Th(−), but all were Th(+). The sample is too small to be meaningful.

The family data are consistent with the hypothesis offered above, namely, that Bu detects a Gm(b) antigen produced by the Gm^b and Gm^{ab} alleles but not by the Gm^{abc}, Gm^a, or Gm^{ax} alleles, and that Th detects a Gm(b) antigen which is always produced by the Gm^b allele, usually produced by the Gm^{ab} allele, and sometimes produced by a Gm^a allele but not by the Gm^{abc} or Gm^{ax} alleles.

TABLE 6. REACTIONS WITH ANTISERA TH AND BU‡ OF SERUM SAMPLES OF KNOWN GM PHENOTYPES FROM VARIOUS MONGOLOID POPULATIONS

Population	Total no. tested	Phenotypes*† a No.	a % Th(+)	ax No.	ax % Th(+)	abb^w No.	abb^w % Th(+)	abxb^w No.	abxb^w % Th(+)
Japanese	166	88	62.5	43	25.6	29	100	6	100
Chinese-Mainland	100	23	52.2	12	33.3	49	100	16	100
Chinese-Taiwan	100	4	100	2	100	87	100	7	100
Athabascan Indians	64	38	31.6	23	26.1	3	100	0	0
Eskimos-Alaska	38	28	42.9	3	0	7	100	0	0

*The generic name of the locus *(Gm)* is omitted.
†The phenotypes were determined with the standard reagents listed in Table 1.
‡All b(−) individuals were Bu(−); all b(+) individuals were Bu(+).

Population Data

It will be recalled that none of the 33 Gm(b−) samples in the white panel was Th(+). This raises a question concerning the source of the Th(+) Gm^a allele in the serum samples of the American Negro panel and of the Brazilian families. The surmise is that the source is the American Indian ancestry known to be present in the Brazilian families and reputedly present in the ancestry of the American Negro.

A summary of tests done on various Mongoloid populations and on African Negroes, Australian aborigines, and Melanesians is presented in Tables 6 and 7. It is striking that Th(+) Gm^a alleles occur in all of the Mongoloid populations and in none of the others. We may conclude that Indian ancestry is the source of this allele in the American Negro and in the Brazilian families.

The source of the Th(−) Gm^{a^b} allele in the Brazilian families and in the American Negro panel would appear to be the African Negro ancestors of these people (Table 7). No evidence for a Th(−) Gm^{a^b} allele was found in any of the Mongoloid populations, but the number of Gm(b+) samples was small. More tests are required of these and other populations before we may conclude that Th(−) Gm^{a^b} alleles do not occur in these populations. For the present, however, it is reasonable to assume that the African Negro is the source of the allele.

The data thus far presented suggest that the reactions of the Gm alleles of the various races are as shown in Table 8.

Families with Unusual Phenotypes

The data from eight Brazilian families (not included in Table 6), who presented unusual phenotypes with respect to the three antibodies Da, Th, and Bu, are presented in Table 9.

Three families (491, 653, and 945) present strong evidence for the presence of a Gm allele negative for Gm(a) and Gm(b) but positive for the antigens detected by Da and Bu. Such alleles would, by former criteria, be classified as Gm^- (Nielsen and Henningsen, 1961; Steinberg, 1962a; Ropartz, Rivat, and Rousseau, 1962). Thus, in family 491, the father's phenotype is

TABLE 7. REACTIONS WITH ANTISERA TH AND BU* OF SERUM SAMPLES OF KNOWN GM PHENOTYPES FROM THE INDICATED POPULATIONS

Population	Total no. tested	Phenotypes† a No.	a % Th(+)	ax No.	ax % Th(+)	ab No.	ab % Th(+)	abc No.	abc % Th(+)	abb^w No.	abb^w % Th(+)
African Negroes	106	0	–	0	–	50	100	56	84	0	–
Australian Aborigines	37	23	0	12	0	0	–	0	–	2	100
Melanesians-New Guinea	50	28	0	0	–	22	100	0	–	0	–

*All Gm (b+) individuals except four of the 56 Gm(a+b+c+) Negro individuals were positive with antiserum Bu, and all Gm(b–) individuals were negative with this antiserum; hence, the details of the reaction with antiserum Bu are not listed in the table.

†The phenotypes were determined with the standard reagents listed in Table 1.

TABLE 8. USUAL REACTIONS OF THE GM FACTORS PRODUCED BY DIFFERENT GM ALLELES WITH THE ANTIBODIES DRAVES, DA, TH, AND BU

Race	Allele	Draves	Da	Th	Bu
Caucasoids	Gm^a	–	–	–	–
	Gm^{ax}	–	–	–	–
	Gm^b	+	+	+	+
Negroids	Gm^{ab}	+	–	+*	+
		+	–	–†	+
	Gm^{abc}	+	–	–	–
Mongoloids	Gm^a	–	–	–*	–
		–	–	+†	–
	Gm^{ax}	–	–	–	–
	Gm^{ab}	+	+	+	+

*The more common reaction.

†The less common reaction.

Gm(a–b+c–x–) and therefore his genotype is presumably Gm^b/Gm^b. But he had three children who were Gm(a+b–c–x–), i.e., children who did not receive an allele producing Gm(b). There is no evidence to indicate they are extramarital. Therefore, the father must have an allele which does not produce Gm(a) or Gm(b), as detected by the standard reagents, but which is Da(+), Th(+). In family 653, the father has a Gm^{abc} allele, since he is Gm(a+b+c+) (Steinberg and Wilson, 1963a). He has one Gm(a–b+c–x–) and two Gm(a+b–c–x–) children. This implies that he has a Gm^a and a Gm^b allele in addition to the Gm^{abc} allele, a total of three alleles! Again, if these children are not extramarital, a more reasonable explanation is that he has an allele which produces neither Gm(a) nor Gm(b). In family 945, the question of paternity does not arise since it is the mother who has the unusual allele. This conclusion is based on the presence of a Gm(a–b+c–x–) child and on the mother's phenotype, Gm(a+b–c–x–), as shown in Table 9. As mentioned above, in each of these three families, there is strong evidence for an allele which produces the antigens detected by the antisera Da and Th but not those detected by the standard anti-Gm(a) and anti-Gm(b) antibodies. Weaker evidence for this allele is presented by family 169. The unusual allele in this family could be Gm^a, positive with Da and Th.

TABLE 9. FAMILIES WITH UNUSUAL PHENOTYPES WITH RESPECT TO ANTIBODIES DA, TH, AND BU

Family		Gm phenotype*†	Da	Th	Bu	Probable genotype*
A. Families with a Da(+) Th(+) *Gm*− allele (see text).						
491	Fa	b	+	+	+	*b*/− [Da(+)Th(+)]
	Mo	abc	−	−	−	*abc/a*
	4‡	ab	+	+	+	*a/b*
	3‖	a	+	+	−	*a*/− [Da(+)Th(+)]
653	Fa‖	abc	+	+	−	*abc*/− [Da(+)Th(+)]
	Mo	ab	+	+	+	*a/b*
	1	b	+	+	+	*b*/− [Da(+)Th(+)]
	1	abc	+	+	+	*abc/b*
	2‖	a	+	+	−	*a*/− [Da(+)Th(+)]
945	Fa	abx	+	+	+	*ax/b*
	Mo	a	+	+	−	*a*/− [Da(+)Th(+)]
	2‖	ax	+	+	−	*ax*/− [Da(+)Th(+)]
	1	ab	+	+	+	*a/b*
	1	b	+	+	+	*b*/− [Da(+)Th(+)]
169	Fa‖	a	+	+	−	*a*/− [Da(+)Th(+)]§
	Mo	ab	+	+	+	*b/a* [(Th+)]§
	3‖	a	+	+	−	*a*/− [Da(+)Th(+)] or *a*[(Th+)]/− [Da(+)Th(+)]
	1	a	−	+	−	*a/a* [(Th+)]
B. Family with a Bu(+) *Gm*− allele or a *Gm*^{b} allele negative with Da and Th (see text).						
224	Fa	b	+	+	+	*b*/− [Bu(+)]
	Mo	abc	+	+	+	*abc/b*
	1‖	abc	−	−	+	*abc*/− [Bu(+)]
	2	abc	+	+	+	*abc/b*
	2	b	+	+	+	*b*/− [Bu(+)]
C. Family with a Th(−) *Gm*^{b} allele or Da(+), Th(−), *Gm*^{ab} allele (see text).						
910	Fa	a	−	−	−	*a/a*
	Mo‖	ab	+	−	+	*a/b* [Th(−)] or *a/ab* [Da(+)Th(−)]
	2	a	−	−	−	*a/a*
	3‖	ab	+	−	+	*a/b* [Th(−)] or *a/ab* [Da(+)Th(−)]
D. Family with a Da(+) *Gm*^{abc} allele (see text).						
167	Fa	ax	−	−	−	*a/ax*
	Mo‖	abc	+	−	−	*a/abc* [Da(+)]
	3‖	abc	+	−	−	*a/abc* [Da(+)]
	1‖	abxc	+	−	−	*ax/abc* [Da(+)]
	1	a	−	−	−	*a/a*
	1	ax	−	−	−	*a/ax*
E. Family with a *Gm*− allele (see text).						
227	Fa	b	+	+	+	*b*/−
	Mo	ab	+	+	+	*a/b*
	6	a‖	−	−	−	*a*/−
	3	ab	+	+	+	*a/b*
	1	b	+	+	+	*b/b* or *b*/−

*The generic name of the locus (*Gm*) is omitted.

†The phenotypes were determined with the standard reagents listed in Table 1.

‡The number indicates how many offspring had the indicated phenotype.

‖Unusual phenotype.

§Alternative genotypes: Fa: *a*(Th+)/− Da(+)Th(+); Mo: *a/b* etc.

TABLE 10. REACTIONS OF GM ALLELES IN VARIOUS RACES WITH ANTI-GM(a), ANTI-GM(b), ANTI-GM(c), ANTI-GM(x) AND ANTIBODIES DA, TH, AND BU

Allele	Antisera						
	a	b	c	x	Da	Th	Bu
			Negroids				
*ab**	+	+	−	−	−	+	+
ab(Th−)	+	+	−	−	−	−	+
abc	+	+	+	−	−	−	−
			Mongoloids				
a	+	−	−	−	−	−	−
a(Th+)	+	−	−	−	−	+	−
ax	+	−	−	+	−	−	−
ab	+	+	−	−	+	+	·:·
			Caucasoids				
a	+	−	−	−	−	−	−
ax	+	−	−	+	−	−	−
b	−	+	−	−	+	+	+

*The generic name of the locus (*Gm*) is omitted.

Family 224 offers evidence for a Bu(+) "Gm^-" allele, but a Da(−), Th(−), Bu(+) Gm^b allele could explain the data equally well.

The data for family 910 may be interpreted in either of two ways, as shown in Table 9. One interpretation indicates a Gm^b allele negative with Th; the other a Gm^{ab} allele which is positive with Da. There is little to choose between the alternative interpretations on the basis of the present data.

The data for family 167 indicate the presence of a Da(+) Gm^{abc} allele. According to her Gm(a+b−c−x−) and her Gm(a+b+c−x+) offspring, the mother's phenotype results from heterozygosity for Gm^{abc}/Gm^a alleles. Nevertheless, she and her four children who received her Gm^{abc} allele are positive for the antigen(s) detected by Da, while her two children who did not receive her Gm^{abc} allele and her husband are negative for the antigen(s) detected by Da.

Family 227 offers strong evidence for an allele negative with all our reagents, in brief a Gm^- allele. This conclusion rests on the observation that a Gm(a−b+c−x−) father had six Gm(a+b−c−x−) offspring. These offspring indicate that the father has an allele which produced neither Gm(a) nor Gm(b). Since these children lack the antigens detected by antibodies Da, Th, and Bu, it follows that the allele inherited from the father does not produce these antigens.

DISCUSSION

The data raise questions concerning the relation of the Da, Th, and Bu antibodies to each other and to those commonly used to define Gm(a), Gm(b), Gm(x), and Gm(c).

A summary of the reactions of the "common" alleles in each of the three races here considered is presented in Table 10. It is of interest, because nomen-

clature may confuse interpretation, to consider how the alleles might have been named had the Gm factors been found first in Negroids or Mongoloids rather than in Caucasoids.

Suppose the seven antibodies listed in Table 10 had first been tested in Negroes. Anti-Gm(a) and anti-Gm(b) would probably have been discarded, because they were inhibited by all sera. Anti-Gm(x) and antibody Da would probably also have been discarded, because no sera inhibited them. The factor detected by antiserum Bu might have been called Gm(a) while that detected by antiserum Th might have been called Gm(x), by analogy with our present system of nomenclature. Anti-Gm(c) would, by the same analogy, be Gm(b). If the reagents were first tested with sera from Mongoloids, anti-Gm(a) would probably have been discarded, because all sera inhibited it, and anti-Gm(c) because none did. Antiserum Th would have been considered anti-Gm(a). Anti-Gm(b) would be considered the same as antisera Da and Bu and all three would have been considered to detect Gm(x). Anti-Gm(x) would be considered to detect Gm(b) and what is now considered to be the Gm^a allele would be called a silent allele (Gm^-) because it would not be detected by any of the retained antisera, i.e. anti-Gm(b), Da, Th, Bu, and anti-Gm(x). Finally if the tests were done on Caucasoids only, Gm(b) and antibodies Da, Th, and Bu would all be considered the same. Anti-Gm(a) and anti-Gm(x) would, of course, remain unchanged.

We have presented this exercise in nomenclature to emphasize that the names assigned to the factors are not of great significance and that the strict relations we observe in limited studies may be very different in more broadly based studies. Nevertheless, standards of usage have been established and we shall adhere to them.

Since the antibodies Da, Th, and Bu all detect Gm(b) in whites, we shall consider that they detect antigens produced by the Gm^b allele. The data presented in Tables 9 and 10 indicate that at least four antigens are associated in various combinations with the Gm(b) factor. We shall call these antigens Gm(b^1), Gm(b^2), etc. The antibody which detects the so-called standard Gm(b) in all races and with all alleles which produce it (Draves in this report; however, see below) will be said to detect antigen Gm(b^1) and perhaps others. Antibody Da will be said to detect antigen Gm(b^2). That this antigen is different from those detected by antibodies Th and Bu is demonstrated by the families in sections C and D of Table 9. Antibody Th will be said to detect antigen Gm(b^3), and antibody Bu will be said to detect antigen Gm(b^4). The reactions of the more common alleles in the three races to these antibodies in terms of this nomenclature and a suggested terminology for the alleles are shown in Table 11. No significance is implied by the sequence of numbering the antigens detected by the antibodies.

As tests with other reagents are compared with these, new numbers may be added. Note that in this system of nomenclature the Gm^a Th(+) allele of Mongoloids becomes $Gm^{ab(3)}$.

The Gm phenotypes of the donors of the "Gm(b)" antibodies Draves, Da, Th, and Bu were determined after absorbing aliquots of their sera three times with cells coated with the appropriate anti-D (see Table 1). Their Gm

TABLE 11. REACTIONS OF THE MORE COMMON ALLELES IN NEGROIDS, MONGOLOIDS AND CAUCASOIDS WITH THE GM(b) ANTIBODIES AND A SUGGESTED NOMENCLATURE

Race	Allele: Current terminology	Allele: Suggested terminology	Antibody: Draves Antigen detected: Gm(b^1)	Da Gm(b^2)	Th Gm(b^3)	Bu Gm(b^4)
Negroid	Gm^{ab}	$Gm^{ab(1,3,4)}$	+	−	+	+
	Gm^{ab}	$Gm^{ab(1,4)}$	+	−	−	+
	Gm^{abc}	$Gm^{ab(1)c}$	+	−	−	−
Mongoloid	Gm^{a}	Gm^{a}	−	−	−	−
	Gm^{a}	$Gm^{ab(3)}$	−	−	+	−
	Gm^{ax}	Gm^{ax}	−	−	−	−
	Gm^{ab}	$Gm^{ab(1,2,3,4)}$	+	+	+	+
Caucasoid	Gm^{a}	Gm^{a}	−	−	−	−
	Gm^{ax}	Gm^{ax}	−	−	−	−
	Gm^{b}	$Gm^{b(1,2,3,4)}$	+	+	+	+

phenotypes are as follows (only positive reactions are recorded): Draves, Gm(ax); Da, Gm(a,$b^{1,3,4}$); Th, Gm(a,b^1c); Bu, Gm(a). The donors of antibodies Da and Th are Negroes, and each exhibits a common Negro phenotype. Da produced an antibody against the only Gm(b) antigen he lacked. His mother has this antigen (Steinberg and Wilson, 1963 a, b). The others produced antibodies against only one of the three or four antigens which they lacked.

The Gm(b^1) antigen seems to be the most common of the Gm(b) antigens and corresponds to the Gm(b) reported by Harboe (1959).

There are 16 possible patterns of reactions to the four antibodies defining the four Gm(b) antigens. Eleven of them have been observed, six commonly (Table 11) and five rarely [Table 9 and two examples of a $Gm^{b(2)}$ allele found in a reanalysis of Hutterite families 61.10 and 151.07, previously reported as having a Gm^- allele (Steinberg 1962a)]. The five which have not been observed are listed in Table 12. There is no simple scheme of relationship among the observed reaction patterns, except that when a serum is positive with Da(b^2) it is usually positive with the other three reagents, although exceptions occur (Table 9). A second pattern is that the Gm(b^4) antigen, detected by Bu, is invariably present when antigens Gm(b^1) and Gm(b^3) are present; if either is absent, Gm(b^4) may or may not be absent. Clearly, further studies of these and other antibodies are required before a satisfactory immunological interpretation can be reached.

These reagents have served to distinguish the Gm^{ab} allele of Mongoloids from that of Negroids and to demonstrate a heterogeneity among the Gm^{ab} alleles of the latter and among the Gm^{a} alleles of the former. Thus, they have increased the usefulness of the Gm system for characterizing the races of man. Similarly, they have increased the usefulness of this locus for linkage studies and for application to medico-legal problems. Gm(b^w), now called Gm(b^2), has proven useful for the study of the relation of the Gm antigens

TABLE 12. POSSIBLE PATTERNS OF REACTIONS WITH FOUR GM(b) ANTISERA WHICH HAVE NOT YET BEEN OBSERVED

Antibody: Gm(b) Antigen:	Draves (1)	Da (2)	Th (3)	Bu (4)
	+	+	+	−
	+	−	+	−
	−	+	+	+
	−	+	−	+
	−	−	+	+

to the structure of 7S γ-globulin (Polmar and Steinberg, 1964). It is reasonable to assume that the others will also prove useful for further detailed studies of this molecule.

SUMMARY

Four antibodies which detect Gm(b) in whites were used for family and population studies on serum samples from individuals of Negroid, Mongoloid, or Australoid ancestry and from individuals of mixed Caucasoid, Negroid, and Mongoloid ancestry.

Confining our remarks to the Gm(b) factor, these studies showed (1) that the Gm^b allele of whites leads to the production of at least four antigens, called Gm(b^1), Gm(b^2), Gm(b^3), and Gm(b^4), respectively; (2) that the Gm^{ab} allele in Negroes can be subdivided into two alleles, one which produces antigens Gm(b^1), Gm(b^3), and Gm(b^4) and one which produces Gm(b^1) and Gm(b^4); (3) that the Gm^{abc} allele of Negroes produces only the Gm(b^1) antigen; (4) that the Gm^{ab} allele of Mongoloids produces all four Gm(b) antigens; and (5) that Mongoloids have a Gm^a allele which produces Gm(b^3) in addition to Gm(a). It is suggested that this allele be called $Gm^{a\,b(3)}$ rather than Gm^a. Some rare alleles produce other combinations of the Gm(b) antigens (see Tables 9 and 11).

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APPENDIX

Data from 18 randomly selected families of mixed white, Negro, and South American Indian ancestry, showing discordance between their reactions with antisera Draves, Da, Th, and Bu.

Family		Phenotype*†	Da	Th	Bu
4	Fa	ab	−	−	+
	Mo	abx	+	+	+
	3‡	ab	+	+	+
	2	abx	−	−	+
14	Fa	ab	+	+	+
	Mo	abc	−	+	+
	1	abc	−	+	−
16	Fa	ab	−	−	+
	Mo	abx	−	+	+
	2	ab	−	+	+
42	Fa	a	−	+	−
	Mo	ab	+	+	+
	3	ab	−	+	+
	3	ab	+	+	+
61	Fa	ab	+	+	+
	Mo	ab	−	−	+
	6	ab	+	+	+
66	Fa	abc	−	+	+
	Mo	ab	−	+	+
	3	abc	−	−	+
	2	abc	−	+	+
	3	ab	−	+	+
74	Fa	abc	−	+	−
	Mo	b	+	+	+
	4	ab	+	+	+
	1	abc	+	+	+
79	Fa	ax	−	+	−
	Mo	a	−	+	−
	1	ax	−	−	−
94	Fa	ab	+	+	+
	Mo	abx	−	+	+
	1	abx	+	+	+
	1	abx	−	−	+
	1	ab	−	+	+
	2	ab	+	+	+

APPENDIX (CONTINUED)

Family		Phenotype*†	Da	Th	Bu
102	Fa	ab	−	+	+
	Mo	ab	−	+	+
	6	ab	−	+	+
	1	a	−	+	−
110	Fa	ab	+	+	+
	Mo	abc	−	+	−
	1	abc	+	+	+
	1	abc	−	+	+
	2	ab	−	+	+
	1	ab	+	+	+
117	Fa	ab	+	+	+
	Mo	ab	+	+	+
	1	ab	−	−	+
	2	ab	+	+	+
	1	b	+	+	+
129	Fa	b	+	+	+
	Mo	ax	−	+	−
	2	ab	+	+	+
140	Fa	ab	+	+	+
	Mo	a	−	−	−
	1	ab	+	+	+
	1	a	−	+	−
144	Fa	ab	+	+	+
	Mo	abxc	−	−	−
	2	abc	+	+	+
	1	abc	−	−	−
154	Fa	abx	+	+	+
	Mo	ab	+	+	+
	2	ab	+	+	+
	1	ax	−	+	−
	1	b	+	+	+
162	Fa	b	+	+	+
	Mo	a	−	+	−
	1	ab	+	+	+
163	Fa	ab	−	−	+
	Mo	ab	−	+	+
	2	ab	−	+	+
	1	ab	−	−	+
	1	a	−	−	−

*The generic name of the locus *(Gm)* is omitted.

†The phenotypes were determined with the standard reagents listed in Table 1.

‡This number indicates how many offspring had the listed phenotype.