A Gm-like Factor Present in Negroes and Rare or Absent in Whites: Its Relation to Gm^a and Gm^x[1]

ARTHUR G. STEINBERG, BRENDA DAWN GILES, AND RACHEL STAUFFER

Department of Biology, Western Reserve University, Cleveland, Ohio

GRUBB (1956) FOUND that some human sera contain a factor capable of inhibiting the ability of serum from selected rheumatoid arthritic patients (RA serum) to cause Rh(+) cells coated with selected incomplete anti-D sera to agglutinate. Grubb and Laurell (1956) showed that this factor is contained in the gamma-globulin fraction of serum and therefore named it Gm^a. Individuals having the factor are called Gm(a+), those lacking it Gm(a−). Grubb and Laurell (1956) reported that 59.7 per cent of 360 Swedes and 94.6 per cent of 74 Eskimos were Gm(a+). They showed further that the presence of the factor was probably due to a dominant allele (Gm^a), its absence due to one or more undetected alleles collectively symbolized as *Gm*. The genetic observations were confirmed by Moullec, Kherumian, Sutton, and Espagnon (1956) and by Linnet-Jepsen, Galatius-Jensen, and Hauge (1958).

Moullec *et al.* (1956) reported that work in progress indicated that the newborn infant appeared always to have the same Gm group as its mother. Brønnestam and Nilsson (1957) confirmed this by a study of the Gm factor of 74 mothers and their newborn infants. The infant's Gm reaction was invariably identical with its mother's reaction. Linnet-Jepsen (cited in Linnet-Jepsen *et al.*) studied 165 mother-newborn infant pairs and followed 113 of the infants over a period of months. He reports that the Gm group of the infant does not yet seem to be fully developed at eight months. Grubb and Laurell (1956), Laurell and Grubb (1957), and Linnet-Jepsen *et al.* (1958) offered evidence to indicate that the Gm locus is independent of sex, the Hp groups, secretor, and the ABO, MNS, Rh, P, Lewis, Kell, Lutheran, and Duffy blood groups.

Population studies have been done on 360 Swedes (Grubb and Laurell, 1956), 871 Frenchmen (300 by Moullec *et al.*, 1956, and 571 by Podliachouk *et al.*, 1958), 1,084 Danes (Linnet-Jepsen *et al.*, 1958), 320 Norwegians (Harboe and Lundevall, 1959), and 74 Eskimos (Grubb and Laurell, 1956).

The frequency of Gm(a+) individuals among the European populations ranged from 54.3 (Moullec *et al.* on Frenchmen) to 60.6 (Harboe and Lundevall on Norwegians), but the differences are not significant. A total of 2,635 white individuals were tested in the five studies, and 1,501 (56.96 per cent) of them

Received August 17, 1959.

[1] Supported in part by Research Grant A-1931 from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health.

were Gm(a+). This contrasts with 94.6 per cent Gm(a+) among 74 Eskimos (Grubb and Laurell, 1956).

Harboe and Lundevall (1959) reported a new factor (Gm^x) believed by them to be an allele of Gm^a, although they indicate that their data do not exclude a two-locus hypothesis. They found that 82 (25.8 per cent) of 318 Norwegians were positive for this factor and that it is inherited as a dominant. All Gm(x+) individuals were also Gm(a+); hence, only three phenotypes were observed in their population and in their family data, namely, Gm(a+ x+), Gm(a+ x−), and Gm(a− x−).

More recently Harboe (1959a and b) reported a system which tests for an allele of Gm^a whose frequency could account for the Gm(a−) class originally reported by Grubb and Laurell. This allele is called Gm^b (Harboe, 1959b).

In 1958 we decided to test an American Negro population to determine the frequency of Gm(a+) individuals among them. Accordingly, we attempted to find appropriate RA and anti-D sera to detect Gm^a. This paper is a report of our investigations.

MATERIALS AND METHODS

Sera from patients suffering from rheumatoid arthritis were kindly supplied by Dr. Robert Stecher and Dr. Paul Vignos. Anti-D sera were kindly supplied by Dr. Richard Rosenfield, Dr. Russell Weisman, Dr. Roger Marsters, Dr. Eloise Giblett, and Dr. F. H. Allen, Jr. We are grateful to these people for their generous cooperation.

The procedures used for testing were the same as those described by Linnet-Jepsen *et al.* (1958) except that quantities for the tests were measured in drops and, equating one drop to .05 ml., all quantities were halved in later tests. We found also that the Rh(+) cells could be used for at least six days and probably longer. Thirty-five RA sera and 25 anti-D sera were tested (not in all possible combinations, however) to find usable reagents.

Sera from unrelated white and Negro individuals were obtained from the routine hematology laboratory of the University Hospitals Out-Patient Department. Sera for family studies were obtained from families being investigated in other genetic studies in this laboratory.

THE DATA

We did not succeed in finding a pair of sera (RA-anti-D) giving the Gm^a reaction, but we did find relatively early in our testing an RA serum (Bomb.) from a white patient, which when used at a dilution of 1:20 in saline with an anti-D (Warren) from a Negro patient used at a dilution of 1:10 in saline gave an easily readable and reproducible reaction system.

This system has now been tested against 250 adult whites and against 403 adult Negroes with the results shown in Table 1. It is apparent that the factor is absent or rare among whites (P of observing none positive among 250 ~ .005 if the frequency is as high as .02; and ~.1 if the frequency is as low as about .01). It occurs with a frequency of .275 ± .022 among Negroes. Dr. Sylvia Lawler

TABLE 1. FREQUENCY OF THE GM-LIKE FACTOR AMONG NEGROES AND WHITES

	Total	Gm-like			
		+		−	
		No.	%	No.	%
Adult Negro population	265	73	27.5	192	72.5
Negro parents of the families studied	138	38	27.5	100	72.5
Total adult Negroes	403	111	27.5	292	72.5
Whites	250	0	—	250	100.0

TABLE 2. SUMMARY OF TESTS OF NEGRO FAMILIES FOR THE GM-LIKE FACTOR

Both Parents +					One Parent +					Neither Parent +			
Offspring					Offspring					Offspring			
s	r	n_{sr}	+	−	s	r	n_{sr}	+	−	s	r	n_{sr}	−
2	0	2	4	0	1	1	2	0	2	1	1	3	3
3	1	1	2	1	2	0	1	2	0	2	2	9	18
	2	1	1	2		1	5	5	5	3	3	5	15
5	0	1	5	0		2	3	0	6	4	4	7	28
6	0	1	6	0	3	1	4	8	4	5	5	4	20
						2	3	3	6	6	6	6	36
Total		6	18	3	4	2	3	6	6	7	7	2	14
					5	1	1	4	1	8	8	1	8
					6	2	1	4	2				
					7	4	1	3	4	Total		37	142
					8	4	2	8	8				
					Total		*26	43	44				

s = number in sibship.
r = number who are Gm-like negative.
* In 13 families the father was + and the mother −, and in 13 the mother was + and the father −.

of the Galton Laboratory kindly confirmed our testing for this factor by retesting 12 serum samples with our reagents.

Studies of Negro families were done to establish the pattern of inheritance. A summary of the data is presented in Table 2. We note in passing that the families were typed for secretor and the ABO, MN, Rh, Kell, Duffy, Jk, Js, Lu, and P blood groups. They were tested also for haptoglobins (Hp) and transferrins (Tf) by Dr. Eloise Giblett. If, on the basis of any of these tests or by the mother's admission, a child was shown to be extra-marital the family was not included. Nevertheless, it is possible that some families with extra-marital children have been included. The blood group, Hp, and Tf data will be reported at a later date.

The observed and expected numbers of matings in which both, one, or neither

TABLE 3. OBSERVED AND EXPECTED NUMBERS OF MATINGS IN WHICH BOTH, ONE, OR NEITHER PARENT IS GM-LIKE POSITIVE

Number of Parents +	Observed	Expected
2	6	5.2
1	26	27.5
0	37	36.2
Total	69	68.9

parent is positive are shown in Table 3. (The expected numbers were computed on the basis of 111 positive in a total of 403.) We may conclude that mating is random for this character.

ANALYSIS OF THE FAMILY DATA

The data in Table 2 indicate that when neither parent is positive for the Gm-like factor, none of the children is positive. The probability that 142 children would be negative by chance = $(.725)^{142}$ or $\sim 1.5 \times 10^{-10}$. This observation and the indication in Table 2 that more children are positive when both parents are positive than when only one parent is, suggests that the presence of the factor may be due to a dominant gene.

This may be tested (a) by computing the expected number of segregating (families with at least one recessive child) and of non-segregating families among those in which at least one parent is positive and (b) by estimating the proportion of recessives among the offspring of the segregating families and comparing the estimate with the expected proportion. The former test was done with the aid of the tables published by C. A. B. Smith (1956); the latter was done by the maximum likelihood method with the aid of the tables published by Finney (1949).

There were six matings in which both parents were positive and two of these were segregating (Table 2). The expected number is 3.06 (variance 1.4059). There were 26 matings in which only one parent was positive and 25 of these were segregating. The expected number is 19.89 (variance 4.2957). The difference is significant ($P \sim .017$); but the sample is small, and the deviation is in the opposite direction to that found for families in which both parents were positive. When both sets of matings are combined, the expected number of segregating families is 22.9 ± 2.39 and the observed 27. The difference is not significant ($P \sim .09$).

The maximum likelihood estimate of the proportion of recessive offspring in segregating families with one parent positive is $.43 \pm .06$; the expected value is .50, hence the difference is not significant.

We conclude that the Gm-like factor is due to a dominant gene. Its frequency in American Negroes is $.149 \pm .013$. It is absent or very rare in American whites.

The deficit of Gm-like(+) children from segregating matings with one parent positive (.43 rather than .50) cannot be explained by assuming that, as in Gm^a, children do not express their genotype until some time after birth. The age distribution of children with mothers positive is the same as that with

TABLE 4. TESTS OF SERA FROM NEGROES FOR GM-LIKE AND FOR Gm^a

	Gm^a		
Gm-like	+	−	Total
+	28	0	28
−	68	2	70
Total	96	2	98

mothers negative, and direct observation shows that in the former case, 22 children were positive and 23 were negative, while in the latter, 21 were positive and 21 negative.

We have not yet tested newborn infants and their mothers, but we have observed an eight-month old Gm-like(+) infant whose mother was Gm-like(−). We have also observed several one- and two-year olds whose Gm-like type differed from their mothers'. We have not examined enough very young children to be able to evaluate the data quantitatively.

RELATION OF GM-LIKE FACTOR TO Gm^a

Through the generosity of Dr. Sylvia Lawler, Dr. Hugh Fudenberg, and Dr. Morten Harboe, we obtained reagents to test for Gm^a.

Sera from 98 Negroes were tested for Gm-like and for Gm^a. Only two were Gm(a−) and both were also Gm-like(−) (Table 4). The probability that the distribution may have arisen by chance, assuming independence of Gm^a and Gm-like, is .51.

The expected frequency of Gm-like(+), Gm(a−), assuming they are independent, is approximately .0056 (.02 × .28). Only about 2 in 1,000 matings may be expected to be between an individual heterozygous for Gm-like and Gm^a and an individual negative for both, again assuming independence of the two factors. Clearly, it will require an enormous sample or extraordinary good luck to determine the genetic relation between these two factors.

There seems little to be gained by outlining a series of possible relations between these two factors. The more likely ones are obvious, and none can be evaluated with our present data.

RELATION OF GM-LIKE TO Gm^x

Dr. Morten Harboe kindly sent us samples of his reagents to test for Gm^x.

After establishing that we could duplicate his findings with the control sera he sent to us, we tested the sera of Negroes for Gm^x. During the course of this testing we found that an anti-D serum (M-18), of which we had only a small supply, and an RA serum (Bowers) duplicated the Gm^x test. With these reagents and those supplied by Dr. Harboe, we were able to test sera from 75 unrelated Negroes. The data are presented in Table 5. It is clear that Gm-like and Gm^x are not the same, and that Gm^x is much rarer in Negroes than in whites. As in the case of Gm^a, it well require a large sample to enable us to determine the genetic relation between these two factors.

TABLE 5. TESTS OF SERA FROM NEGROES FOR GM-LIKE AND FOR Gm^x

	Gm^x		
Gm-like	+	−	Total
+	0	16	16
−	1	58	59
Total	1	74	75

SPECIFICITY OF THE REAGENTS

Grubb (1958) and Harboe (1959) demonstrated that as a rule only anti-D sera from individuals positive for a particular Gm factor can be used to test for that factor. Harboe (1959) reported that an anti-D serum from a Gm(a+ x+) individual could be used to test for Gm^a with one RA serum and for Gm^x with a different RA serum. Note that the specificity of the reaction is determined by the RA serum. We were able to confirm Dr. Harboe's findings using his reagents.

Experience with RA (Bomb.) demonstrates that the specificity of the reaction does not necessarily reside in the RA serum. Dr. Sylvia Lawler, to whom we sent RA (Bomb.) and anti-D (Warren) (the reagents used to test for Gm-like), found that RA (Bomb.) and her anti-D (1386) tested for Gm^a. Here then is an RA serum which can test for two factors, with the specificity being determined by the anti-D. We were able to confirm and to extend these observations with RA (Bomb.) and with RA (Bowers). A summary of our findings, which will be presented in detail elsewhere, is given in Table 6.

RA (Bowers) may be used to test for Gm^a and Gm^x, the specific factor being determined by the anti-D used. We found that RA (Bomb.) may be used not only to test for Gm^a and Gm-like, but also for Gm^b, depending upon the anti-D used. [The findings on RA (Bomb.) have been independently confirmed by Harboe (personal communication).] Thus we now have two RA sera which can detect more than one RA system, and with the specificity being determined by the anti-D serum rather than the RA serum.

In parallel with Harboe's findings we observed that the specificity for anti-D (Kimb.) and for anti-D (Ham.) in the Gm reaction is conferred by the RA serum used (Table 6). But note that anti-D (Kimb.), which can detect Gm^a or Gm^b, detects Gm^b with RA (Bomb.), although RA (Bomb.) can detect Gm^a

TABLE 6. RA-ANTI-D SYSTEMS USED TO TEST FOR VARIOUS GM FACTORS
(The Gm factors are listed in the body of the table.)

Anti-D (Source)	RA (Bowers)	RA (Bomb.)
Kimb. (B.G.L.)	a	b
Ham. (B.G.L.)	x	b
1386 (Lawler)	—	a
And. (Giblett)	—	b
Warren	—	Gm-like

— = not tested.

when used with anti-D (1386) and with some other anti-D sera not listed in Table 6. Hence an anti-D serum which serves to detect Gm^a with one RA serum may not do so with another RA serum even though the latter may be used to detect Gm^a with a second anti-D (Table 6). Clearly, the specificity resides in the RA-anti-D system as such and not in either alone, although it does appear that the anti-D donor must have the factor for which the anti-D is used to test. It does not follow, however, that if the donor has the factor the anti-D is necessarily usable. It seems on the other hand that the donor of the RA serum need not have the factor being tested for. We say this because Mrs. Bomb., the donor of the RA used to test for Gm-like, is white. The reader will recall that none of the 250 whites was positive for Gm-like. Further discussion of the nature of the Gm reagents will be reserved until investigations now in progress have been completed.

Grubb (1958) reported that various methods of analysis show that the Gm^a factor is located in the gamma globulin fraction and that the inhibiting capacity of Gm(a+) sera varies with the gamma globulin concentration. This suggests that Gm(a+ x+) individuals may differ only quantitatively from Gm(a+ x−) individuals because no Gm(a− x+) individuals have been reported (Harboe and Lundevall, 1959). It suggests also that the high frequency of Gm(a+) among American Negroes may be due to the relatively higher concentration of gamma globulin in their serum. By extension of this argument it would appear that Negroes who are Gm-like(+) should have the highest gamma globulin content in their serum. The fact that none of the 16 Gm-like(+) Negroes who were tested for Gm^x was Gm(x+) and that the only Gm(x+) Negro was Gm-like(−) argues against merely quantitative differences among these factors. Further evidence that the differences among the factors are qualitative is derived from the data in Table 6. We refer to the observations that one RA serum may distinguish as many as three Gm factors and that one anti-D may distinguish at least two Gm factors.

SUMMARY

A new serum factor (Gm-like) detected by means of an RA serum-anti-D serum system similar to the one used to detect Gm^a is described. The factor was present in 27.5 per cent of 403 Negroes but in none of 250 whites. It is inherited as a dominant.

Only two of 98 Negroes tested for Gm^a were Gm(a−). Both were also Gm-like(−). We do not have data to evaluate the relation of Gm-like to Gm^a.

Only one of 75 Negroes tested was Gm(x+). He was Gm-like(−). Again, we do not have data to evaluate the relation between Gm-like and Gm^x beyond establishing that they are different.

Evidence is offered to show that the specificity of the reaction testing for the Gm factors lies in neither the RA nor the anti-D serum used, but in both as a reacting system.

REFERENCES

BRØNNESTAM, R., AND NILSSON, S. B. 1957. Gamma globulin groups (Gm) of mothers and their new-born infants. *Vox Sang.* 2 n.s.: 316–319.

FINNEY, D. J. 1949. The truncated binomial distribution. *Ann. Eugen.* 14: 319–328.

GRUBB, R. 1956. Agglutination of erythrocytes coated with incomplete anti-Rh by certain rheumatoid arthritic sera: the existence of other serum groups. *Acta path. microb. scand.* 39: 195–197.

GRUBB, R. 1958. Interactions between rheumatoid arthritic sera and human gamma globulin. *Acta haemat.* 20: 246–252.

GRUBB, R., AND LAURELL, A. B. 1956. Hereditary serological human serum groups. *Acta path. microb. scand.* 39: 390–398.

HARBOE, M. 1959a. A new haemagglutinating substance in the Gm system, anti-Gm. *Nature* 183: 1468–1469.

HARBOE, M. 1959b. A new hemagglutinating substance in the Gm system, anti-Gm^b. *Acta path. microb. scand.* 47: 191–198.

HARBOE, M., AND LUNDEVALL, J. 1959. A new type in the Gm system. *Acta path. microb. scand.* 45: 357–370.

LAURELL, A. B., AND GRUBB, R. 1957. The Hp and Gm groups and secretor characters of 46 blood donors. *Vox Sang.* 2 n.s.: 312–316.

LINNET-JEPSEN, P., GALATIUS-JENSEN, F., AND HAUGE, M. 1958. On the inheritance of the Gm serum group. *Acta genet. et stat. med.* 8: 164–196.

MOULLEC, J., KHERUMIAN, R., SUTTON, E., AND ESPAGNON, P. 1956. Contribution a l'étude du facteur de groupe Gm^a du plasma humaine. *Rev. hémat.* 11: 512–517.

PODLIACHOUK, L., JAQUELINE, F., AND EYQUEM, A. 1958. Le facteur serique Gm^a au cours des rhumatismes inflammatoires chroniques. *Ann. Inst. Pasteur* 94: 590–597.

SMITH, C. A. B. 1956. A test for segregation ratios in family data. *Ann. Eugen.* 20: 257–265.