*Progress in*

# MEDICAL GENETICS

VOLUME II

Edited by

ARTHUR G. STEINBERG

ALEXANDER G. BEARN

PROGRESS IN

# Medical Genetics

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GRUNE & STRATTON

New York and London

1962

Library of Congress Catalog Card No. 60–53514



Printed and bound in U.S.A. (Con–B)

# Foreword

THE PATTERN SET IN THE FIRST VOLUME OF *Progress in Medical Genetics* IS maintained in this volume. Each chapter deals with a specific subject in the field, and in doing so reflects the increasing scope of medical genetics and the frequent necessity of drawing on the specialized techniques developed by allied disciplines.

Ten years ago hereditary biochemical polymorphic systems were almost restricted to the blood group system. Today, several well defined polymorphic systems have been shown to exist among the plasma proteins. Unfortunately, we are still dismally ignorant of the nature of the forces which maintain the polymorphism. Despite this limitation, information has rapidly accumulated concerning the world-wide distribution of the traits concerned and, in some instances, striking headway is being made toward defining the structural differences between the products of allelic genes (Chapters 1–3).

The introduction of chromatography by Martin and Synge in 1941 has made available to the geneticist a convenient and simple tool to investigate the qualitative and quantitative amino acid distribution in body fluids. The results of the successful exploitation of this and subsequent analytical techniques form the subject of Chapter 4.

The application of immunologic principles to the study of the genetics of antibody production has been fruitful not only of new facts but of new concepts. The genetical aspects of modern immunologic theory are critically evaluated in Chapter 5. A clinical extension of this concept has become apparent from the observation of an increased familial concentration of patients suffering from the so-called auto-immune diseases (Chapter 6).

The application of new cytological techniques to the study of human chromosomes has uncovered a remarkable series of chromosomal abnormalities of clinical importance (see Chapter 8, Volume I, of this series). Similar abnormalities have been observed in the chromosomes of other organisms including various mammals whose genetics have been well studied. This affords the investigator an opportunity to study the mode of origin, of transmission, and of action of development of these abnormalities,

in a manner which cannot be done in man. The data may be helpful in interpreting information derived from the study of human chromosomes. Recent progress made in the study of chromosomal aberrations in experimental mammals is reviewed in Chapter 7. The value of an understanding of microbial genetics to students of medical genetics has been amply and justifiably emphasized in recent years. In contrast, the contribution of mammalian genetics has been frequently overlooked, particularly with respect to gene expression. The review of mammalian genetics in Chapter 8 not only considers established knowledge but also the prospects for future developments in this field.

The field of opthalmology has for many years been one of the most productive of the clinical disciplines in the field of genetics, and recent advances in this area form the subject of Chapter 9.

The editors are extremely fortunate in having been able to persuade the authors to contribute to this enterprise. The chapters in this, the second volume of Progress in Medical Genetics, uphold the high standards set by the contributors to the first volume.

A. G. S.
A. G. B.

# Contents

CHAPTER 1

# Progress in the Study of Genetically Determined Human Gamma Globulin Types (The Gm and Inv Groups)

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## INTRODUCTION

GRUBB'S DISCOVERY OF THE GM FACTOR (GRUBB, 1956) IS A REMARKABLE example of serendipity. Grubb wrote, "In the determination of the amount of gamma globulin in sera from six patients with hypogammaglobulinemia by inhibition of the agglutination effect of Coombs' reagent it was observed that one of the sera diluted up to 1:20 in saline agglutinated the red cells coated with 'incomplete' anti-Rh used in this procedure." The serum was from an Rh(+) boy with no anti-Rh, who had acquired hypogammaglobulinemia. As a result of this observation, Grubb ran similar tests on serum samples from several hundred donors (Table 1). Among patients with diseases other than rheumatoid arthritis whose serum agglutinated cells coated with an incomplete anti-D were those with leukemia, cancer, peptic ulcer and the Guillain-Barré syndrome. Grubb classified the agglutinating sera into two broad types: (a) rheumatoid arthritic: these sera yielded firm agglutinates which formed at 18 C. as well as 37 C.,

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This chapter is dedicated with deepest gratitude, admiration and affection to Professor L. C. Dunn, who introduced me to genetics, guided my studies for the Ph.D. and, unknown to him, served as a model of the kind of person I wanted and want to be. All of us who have the good fortune to know him are richer for that experience.

The author's investigations mentioned in this review were supported in part by PHS research grant RG-7214 from the Division of General Medical Sciences, and PHS research grant H-3708 from the National Heart Institute, Public Health Service.

TABLE 1—*Grubb's Data on the Frequency of Occurrence of the Agglutinating Factor in the Serum of Various Donors*

| Serum | | Active | |
|---|---|---|---|
| Donor's Health | No. | No. | % |
| Normal | 333 | 1 | 0.3 |
| Various Ills | 291 | 13 | 4.5 |
| Rheumatoid Arthritis | 51 | 8 | 15.7 |

and had a titer greater than 1/250; the activity of these sera was inhibited by pooled gamma globulin and by about 60 per cent of sera from normal individuals; (b) nonrheumatoid: these sera yielded less firm agglutinates, had a lower titer, were essentially inactive at 37 C., and their activity was not inhibited by pooled gamma globulin.

All the rheumatoid sera which agglutinated the coated cells were positive (at least weakly) for the Waaler-Rose test for the rheumatoid agglutinating factor (RAF), while the nonrheumatoid sera which agglutinated the sensitized red blood cells (SRBC) were negative, or at most weakly positive, in the Waaler-Rose test (Grubb, 1956). Absorption with streptococcus L or O agglutinins did not inactivate the rheumatoid agglutinators, but treatment with bentonite did (Grubb, 1956).

Grubb and Laurell (1956) showed that the ability of sera to inhibit the agglutinating activity of rheumatoid sera is determined by a dominant gene, present in some 60 per cent of the Swedish population and in about 95 per cent of Eskimos. They demonstrated that the inhibitor is located in the gamma globulin fraction of serum and therefore called inhibiting sera Gm(a+), and noninhibiting sera Gm(a−). Grubb and Laurell showed also that the frequency of Gm(a+) is independent of sex and is not affected by pregnancy. All samples were tested for ABO and D; no association was found between them and Gm. Similarly, no association was found between Gm and the MNS, P, Kell, Le and Lu blood type loci in the 30 samples tested for these factors.

It is interesting to note that two other groups of investigators also reported in 1956 that certain sera could cause coated RBC to agglutinate. Waller and Vaughan (1956) reported that 30 of 173 incomplete anti-D sera could be used to sensitize Rh positive cells so that the coated cells were agglutinated by rheumatoid sera and that one of 76 sera from healthy donors also caused the cells to agglutinate. Milgrom, Dubiski and Wozniczko (1956) reported that 10 of 2,000 sera from healthy donors agglutinated RBC coated with incomplete anti-D sera. The titers were as least 1/8. They reported that the agglutinating factors were not inactivated by exposure to 56 C. for 30 minutes, were absorbable by sensitized RBC, and not inhibited by pooled gamma globulin or individual sera.

Heller, Jacobson, Kolodny and Kammerer (1954) found that certain normal sera when used as a diluent for the RA sera in the Waaler-Rose test, inhibited the test. They showed that the inhibitor was in Cohn's F II (i.e., was 7S gamma globulin often referred to as $\gamma_2$-globulin or simply $\gamma$-globulin). Unfortunately, neither they nor anyone else appears to have investigated the matter further.

Moullec, Kherumian, Sutton and Espagnon (1956) confirmed Grubb's brilliant observation that the ability to inhibit the agglutination [Gm(a+)] was determined by a dominant gene which was independent of sex and of the Rh blood type. They showed also that about 54 per cent of Parisian French were Gm(a+).

In 1957 Laurell and Grubb showed that the Gm(a) factor is independent of the haptoglobin types and of the Lewis blood groups. Linnet-Jepsen, Galatius-Jensen and Hauge (1958) confirmed the pattern of inheritance of Gm(a+) and reported that about 56 per cent of 1,284 Danes were Gm(a+), and that *Gm*$^a$ is not associated with the ABO, MNS, Rh, P, Le, K, Lu or Fy blood types or with the Hp locus. They reported also that 68 pairs of identical twins were concordant for Gm(a), but that 18 of 51 pairs of fraternal twins were discordant.

These papers established the existence of the Gm factor and paved the way for investigations on the nature of the inhibitor (the Gm factor), the agglutinator, and the anti-D sera; on the relation of the factor to disease; on the population frequencies of Gm(a); and for the discovery and analysis of other factors. Some work on these problems appeared before 1959, but intensive work on them seems to have begun then. Recent reviews covering various aspects of the problem have been written by Ropartz (1960a) and Grubb (1959b, 1961).

## The Method of Detection of the Hereditary Gamma Globulin Types

The method used to detect the hereditary gamma globulin factors varies slightly from laboratory to laboratory (Ropartz, 1960a), but the basic methodology is the same in all. I will describe the methods usually used in my laboratory.

The reagents commonly used for testing are:

1. Group O red blood cells (RBC) homozygous for the D antigen of the Rh system. We happen to use O $R_1R_1$ cells; others use with equal success O $R_1R_2$ or O $R_2R_2$ cells. Cells heterozygous for the D antigen may be used, but they take up less of the antibody (Masouredis, 1960; Masouredis, Chi and Ferguson, 1960) and therefore give less satisfactory reactions. Unfortunately, the cells from all donors apparently homozygous for the D

antigen are not equally usable, presumably they take up less of the antibody (because of variation in the D antigen?). Only trial can determine whether the cells are adequate.

2. An incomplete anti-D serum of high titer (1/64 or greater) in the Coombs reaction. The anti-D at a concentration of 1/8 should be negative toward cells suspended in saline. Not all incomplete anti-D sera may be used. In all cases thus far reported, the donor of the anti-D is positive for the gamma globulin factor revealed by the use of the anti-D (Grubb, 1957b; Harboe and Lundevall, 1959, and many others), but such positivity does not guarantee that the serum is usable. Here again, the best method for determining the usefulness of a serum is trial. An added complication is the observation that an anti-D which may not be usable with one agglutinating serum (see below) will work excellently with another agglutinating serum (Steinberg, Giles and Stauffer, 1960, and others).

3. An agglutinating serum. These sera are most often found in patients with rheumatoid arthritis (RA), less often in patients with other illnesses and least often in apparently healthy individuals. The reagents from RA patients differ from those from healthy donors in ways which will be discussed in a later section.

In general, the donor of the agglutinating serum is negative for the factor which the serum detects (Grubb, 1958; Laurell and Grubb, 1958; Swahn and Grubb, 1958; Harboe, 1960b), but, as is the case with the anti-D sera, the appropriate Gm or Inv phenotype does not guarantee the usefulness of the serum. Once more only trial can determine this.

The procedure we use to find a system of reagents (agglutinator/anti-D) is to coat the RBC with an anti-D serum (at a 1/10 concentration), and then expose one drop of a 0.3 per cent saline suspension of the washed coated cells to one drop of serum diluted 1/40 if from an RA donor, 1/8 if from a healthy donor. The test is done in a depression of a glass microflocculation test slide. The mixture is shaken (at about 60 r.p.m.) for about five minutes and then placed in a moist chamber (a plastic pan inverted over a wet cloth towel) at room temperature for about 45 minutes. The mixture is then again shaken for about five minutes and the reaction read at 45, 90, or 120× under a dissecting binocular microscope. If the cells are agglutinated, the serum is titrated in serial twofold dilutions against coated cells. Initial trials for gamma globulin typing are done with the agglutinating serum used at a concentration two to four times as great as the minimum concentration giving a three plus agglutination of the cells. Sera of known gamma globulin types diluted 1/4, 1/8, 1/16 and 1/32 are used to test the system. One drop of a given dilution of the test serum is mixed in a well of the slide with one drop of the appropriately diluted agglutinating serum. The mixture is shaken at 60 r.p.m. for about five minutes. One

drop of a 0.3 per cent suspension in normal saline of coated, washed RBC is then added to the mixture. The remainder of the procedure is as described above. Again, trial and error determine the appropriate concentrations of the various reagents (anti-D serum, agglutinating serum, and test sera) to use for a given test.

The tests are performed as follows:

*A. Controls:* Two types of controls are run with each test. One consists of the addition of one drop of the suspension of coated RBC to one drop of normal saline plus one drop of appropriately diluted agglutinating serum, to establish that the agglutinator is active; if it is, the cells will be agglutinated. In the other, the serum to be tested replaces the agglutinating serum. This is to see if the serum to be tested is an agglutinator. If it is not, the cells will remain unagglutinated and the test has meaning. If the cells agglutinate, a new useful agglutinator may have been discovered.

In addition to the above controls, known positive and negative sera are tested to establish that the entire system is working properly.

*B. The typing test:* One drop of appropriate dilutions of the serum to be tested is mixed with one drop of the diluted agglutinating serum. The mixture is shaken for approximately five minutes at about 60 r.p.m., after which one drop of the suspension of the SRBC is added. The mixture is shaken for 5 minutes and then allowed to stand in a moist chamber at room temperature for 40 minutes. It is again shaken for 5 to 10 minutes and then read as described above.

If the cells fail to agglutinate in the presence of the mixture of the tested serum and the agglutinating serum, the former is said to be positive; if the cells agglutinate, the tested serum is negative.

The tests may be illustrated as follows:

| | | *Agglutination* |
|---|---|---|
| | RBC suspended in saline + anti-D → SRBC | − |
| (a) Control 1 | Agglutinator + saline + SRBC | + |
| (b) Control 2 | Test serum + saline + SRBC | − |
| (c) Test | Agglutinator + negative test serum + SRBC | + |
| (d) or | Agglutinator + positive test serum + SRBC | − |

Table 2 lists some examples of the dilutions at which we use various reagents for the Gm and Inv tests. As can be seen from the table, the anti-D/agglutinator combination together determine the gamma globulin factor which will be detected. This will be discussed in a later section.

## The Genetics of the Gm and Inv Factors

Table 3 lists the Gm and Inv factors thus far discovered. Each of the factors has been shown (by the authors first reporting the factors and later

TABLE 2—*Examples of Reagents Used to Test for Various Gamma Globulin Factors*

| | Agglutinator | Dilution | Anti-D | Dilution | Dilutions of Tested Sera |
|---|---|---|---|---|---|
| Gm(a) | Wils. | 1/8 | Kim. | 1/10 | 1/8, 1/16 |
| | Rh 7 | 1/16 | Ham. | 1/10 | 1/8, 1/16 |
| | Bowers | 1/32 | Kim. | 1/20 | 1/16, 1/32 |
| Gm(b) | Bomb. | 1/32 | Ham. | 1/10 | 1/8, 1/16 |
| | Bomb. | 1/128 | Greenway | 1/10 | 1/8, 1/16 |
| | A. Berg | 1/30 | Warren | 1/10 | 1/8, 1/16 |
| Gm(x) | Bowers | 1/48 | Ham. | 1/10 | 1/16, 1/32 |
| | Bowers | 1/64 | Mag. | 1/10 | 1/4, 1/8 |
| Gm-like | Carp. | 1/16 | Warren | 1/5 | 1/16, 1/32 |
| | Bowers | 1/16 | Warren | 1/5 | 1/8, 1/16 |
| | Bowers | 1/16 | 2,147 | 1/10 | 1/8, 1/16 |
| Inv(a) | LeClerc | 1/8 | Roehm | 1/5 | 1/16, 1/32 |
| Inv(b) | Lucas | 1/4 | Ham. | 1/3 | 1/16, 1/32 |

by others) to be inherited as a dominant, or, when properly tested, as a co-dominant.

*A. Caucasoids*

Among Caucasians, Gm(a) and Gm(b) are inherited as alleles (Harboe, 1959; Ropartz, 1960a; Steinberg, 1962a; and others). Gm(x) is usually produced by an allele $Gm^{ax}$ which also produces Gm(a) (Harboe and Lundevall, 1959, and others). But, as we shall see, exceptions occur to both these generalizations. Gm(r) (Brandtzaeg and Mohr, 1961; Brandtzaeg, Fudenberg and Mohr, 1961) thus far appears to be produced by an allele $Gm^{ar}$ which also produces Gm(a), and by an allele $Gm^{arx}$ which produces Gm(x) as well as Gm(a) and Gm(r). Among 356 Gm(a+) Caucasoids about 90 per cent were Gm(r+) and all of 44 Gm(x+) individuals were Gm(r+) (Mohr and Brandtzaeg, 1961). Gm-like has not been shown to be present in Caucasoids, nor is it known whether this factor is deter-

TABLE 3—*Gm and Inv Factors as of December 1961*

| Factor | Reported | Reference |
|---|---|---|
| Gm(a) | 1956 | Grubb and Laurell, 1956 |
| Gm(b) | 1959 | Harboe, 1959 |
| Gm(x) | 1959 | Harboe and Lundevall, 1959 |
| Gm-like | 1960 | Steinberg, Giles, and Stauffer, 1960 |
| Gm(r) | 1961 | Brandtzaeg, Fudenberg, and Mohr, 1961 |
| Inv(a) | 1961 | Ropartz, Lenoir, and Rivat, 1961 |
| Inv(b) | 1962 | Steinberg, Wilson, and Lanset, 1962 |

TABLE 4—*Phenotypes and Genotypes (Usual Alleles Only) Exhibited by Caucasoids*

*A. Gm locus**

| Phenotype a | x | b | Genotype |
|---|---|---|---|
| + | — | — | $Gm^a/Gm^a$ |
| + | + | — | $Gm^{ax}/Gm^{ax}$; $Gm^{ax}/Gm^a$ |
| + | + | + | $Gm^{ax}/Gm^b$ |
| + | — | + | $Gm^a/Gm^b$ |
| — | — | + | $Gm^b/Gm^b$ |

*B. Inv locus*

| Phenotype a | b | Genotype |
|---|---|---|
| + | — | $Inv^a/Inv^a$ |
| + | + | $Inv^a/Inv^b$ |
| — | + | $Inv^b/Inv^b$ |

* Gm(r) has not been included because it has been insufficiently tested and because reagents to test it are not generally available.

mined by an allele of the *Gm* locus or of some other locus (Steinberg, Giles and Stauffer, 1960).

Inv(a) (formerly InV [Ropartz, Lenoir and Rivat, 1961; Ropartz, Rousseau, Rivat and Lenoir, 1961]) was shown on the basis of population studies, to be independent of the Gm locus and of Gm-like (Ropartz, Lenoir and Rivat, 1961; Ropartz, Rousseau, Rivat and Lenoir, 1961). Linkage studies have not yet been done so it can only be said that this factor and Inv(b) (Steinberg, Wilson and Lanset, 1962), are due to alleles at a different locus from the Gm locus and from that causing Gm-like.

The phenotypes and genotypes (common alleles only) among Caucasoids are shown in Table 4. Gm(r) is not shown in the table, because it has been insufficiently tested and because reagents are not generally available to test for this factor.

Table 5 shows the data from 292 white families with 1,724 children tested for Gm(a), Gm(x) and Gm(b) (Steinberg, 1962a, and unpublished data). The data clearly fit the genetic hypothesis outlined above for these three factors.

Henningsen (personal communication) has found a Danish family in which an allele $Gm^{xb}$ seems to be present (Table 6) and Steinberg, Lai, Vos, Singh and Lim (1961) have reported Chinese families in which the allele $Gm^{xb}$ or $Gm^{axb}$ may exist.

Three related families in a religious isolate in the U.S. and a Danish family (Steinberg, 1962a; Nielsen and Henningsen, 1961, respectively)

TABLE 5—*Summary of Gm Data for 292 White Families of a Religious Isolate*[*]

| Mating | No. of Families | Offspring | | | | | |
|---|---|---|---|---|---|---|---|
| | | Total | Phenotypes | | | | |
| | | | a | b | ab | ax | axb |
| ab X b | 102 | 597 | – | 297 | 300 | – | – |
| ab X a | 8 | 40 | 21 | – | 19 | – | – |
| ab X ab | 29 | 200 | 50 | 49 | 101 | – | – |
| ab X axb | 12 | 60 | – | 19 | 13 | 15 | 13 |
| axb X b | 20 | 139 | – | 73 | – | – | 66 |
| axb X axb | 3 | 20 | – | 6 | – | 4 | 10 |
| a X b | 15 | 78 | – | – | 78 | – | – |
| b X b | 91 | 529 | – | 529 | – | – | – |
| a X a | 4 | 28 | 28 | – | – | – | – |
| ab X ax | 3 | 8 | 3 | – | 1 | 2 | 2 |
| ax X b | 3 | 17 | – | – | 6 | – | 11 |
| axb X a | 2 | 8 | – | – | 3 | 5 | – |
| *Total* | 292 | 1,724 | 102 | 973 | 521 | 26 | 102 |

[*] All sera were tested for Gm(a), Gm(x) and Gm(b). Only the positive reactions are listed in the table.

The data include those published in Steinberg, 1962a.

indicate that an allele which produces neither Gm(a) nor Gm(b) exists at the Gm locus (Table 7).

More recently Ropartz, Rivat and Rousseau (1962) have found an Iranian who is Gm(a– b– x–); Inv(a– b+). His gamma globulin level is normal.

*B. Negroids*

Moullec, Fine, Henry and Silverie (1959) reported that all of 449 Negroes from Dakar were Gm(a+). Steinberg, Giles and Stauffer (1960) reported that 96 of 98 American Negroes were Gm(a+) and suggested that miscegenation could explain the occurrence of Gm(a–) individuals among American Negroes. These data would lead one to expect essentially all Negroes to be Gm(b–). Steinberg, Stauffer and Boyer (1960) found, however, that about 98 per cent of 623 American Negroes were Gm(b+). Their data for Negroes and whites tested for Gm(a) and Gm(b) are pre-

TABLE 6—*Family Suggesting a* $Gm^{bx}$ *Allele (Henningsen)*

| | Mother | Father | Children |
|---|---|---|---|
| Phenotypes | abx | b | 3 bx + 3 abx |
| Genotypes | *ax/bx* | *b/b* | *bx/b* *ax/b* |

TABLE 7—*Families Suggesting an Undetected Allele*

| Family | Mother | Father | Children |
|---|---|---|---|
| 61.10* | a | Dead | 3 ab 4 b |
| 68.08* | ab | b | 3 b 3 a |
| 151.07† | a | b | 4 ab 4 a |
| Danish‡ | a | b | 4 ab 2 b |

* Steinberg, 1962a.
† Steinberg, unpublished.
‡ Nielsen and Henningsen, 1961.

sented in Table 8. Steinberg, Stauffer and Boyer (1960) coneluded that Negroes have an allele $Gm^{ab}$ which produces both Gm factors and that Negroes with no white ancestry are all phenotypically Gm(a+ b+). The latter assumption was confirmed by the observations of Ropartz, Rivat and Lenoir (1960b), and of Boyer and Watson-Williams (1961) that all of 708 African Negroes were Gm(a+ b+). On the basis of these assumptions and using the computed frequency of the $Gm^a$ and $Gm^b$ alleles among American Negroes, it was estimated that American Negroes have approximately 31 per cent of white ancestry (the source of $Gm^a$ and $Gm^b$ alleles) (Steinberg, Stauffer and Boyer, 1960). This estimate is almost identical with that reported in 1953 by Glass and Li (30.6 per cent) using the Rh blood groups.

Steinberg, Giles and Stauffer (1960) reported that one of 75 American Negroes was Gm(x+). These authors believe the Gm(x+) resulted from miscegenation, and that Negroes of unmixed ancestry have no Gm(x). This surmise is contradicted by the report by Ropartz, Rivat and Lenoir (1960b) that two of 399 Negroes from Dakar were Gm(x+); however, in a paper presented at the Second International Conference on Genetics (September, 1961), Ropartz stated that Negroes have no Gm(x) factor (Ropartz, Rousseau et Rivat, 1961b). It is possible that Gm(x) oc-

TABLE 8—*Tests of Serum from U. S. Negroes and U. S. Whites for Gm(a) and Gm(b)* (Data from Steinberg, Stauffer and Boyer, 1960)

| | Gm(a+ b+) | | Gm(a+ b—) | | Gm(a— b+) | |
|---|---|---|---|---|---|---|
| Total | No. | % | No. | % | No. | % |
| | | | *A. Negroes* | | | |
| 623 | 593 | 95.2 | 14 | 2.2 | 16 | 2.6 |
| | | | *B. Whites* | | | |
| 249 | 121 | 48.6 | 23 | 9.2 | 105 | 42.2 |

curs rarely among Negroes of unmixed ancestry, but further testing is desirable.

Gm-like (Steinberg, Giles and Stauffer, 1960) has thus far been found only in Negroes although it has been looked for in whites (ibid and unpublished data), Chinese and Indians (Steinberg, Lai, Vos, Singh and Lim, 1961), Japanese (Ropartz, Rivat, Rousseau et Lenoir, 1961), Eskimos, Amerinds (Steinberg, Stauffer, Blumberg and Fudenberg, 1961), and Australian Aborigines (Steinberg, Vos and Kirk, unpublished data). Its relation to the Gm locus is not clear because Negroes tend to be 100 per cent Gm(a+ b+ x−) and therefore show no segregation at this locus.

Ropartz, Rousseau, Rivat and Lenoir (1961) found 53.6 per cent of 399 Negroes from Dakar to be Inv(a+), and Steinberg, Wilson and Lanset (1962) found 52.8 per cent of 329 American Negroes to be Inv(a+). Steinberg et al. (1962) tested 165 Negroes for Inv(a) and Inv(b). Their data are presented in Table 9. They confirmed Ropartz, Rousseau, Rivat and Lenoir's (1961) finding that the Inv locus is independent of the Gm-like locus.

Negroes appear to have only the allele $Gm^{ab}$ at the Gm locus. [They have not been tested for Gm(r).] They have the Gm-like allele also, but, as stated earlier, it is not known how this is related to the Gm locus. Negroes have the alleles $Inv^{a}$ and $Inv^{b}$, and possibly an allele $Inv^{-}$ producing neither Inv(a) nor Inv(b) (Steinberg et al., 1962).

*C. Mongoloids (Chinese, Japanese, American Indians and Eskimos)*

Steinberg, Lai, Vos, Singh and Lim (1961) tested 90 unrelated Chinese from Malaya for Gm(a), Gm(b), Gm(x) and Gm-like. All were Gm-like(−) and Gm(a+). Ninety-three per cent were Gm(b+) and 5.5 per cent were Gm(x+). These data and family data (Steinberg, Lai, Vos, Singh and Lim, 1961) suggest that the Chinese have alleles $Gm^{ab}$, $Gm^{a}$ and $Gm^{ax}$ with frequencies .741, .231 and .028, respectively. Ropartz (personal communication) has tested over 500 Chinese and has found essentially the same frequencies.

Boyer, Iseki and Mayeda (1961) tested 262 Japanese for Gm(a) and Gm(b) and found all Gm(a+) and 22.9 per cent Gm(b+). Ottensooser (personal communication) tested 58 Japanese for Gm(a), Gm(b) and

TABLE 9—*Data for 165 Sera from Negroes Tested for Inv(a) and Inv(b)*
(Data from Steinberg, Wilson and Lanset, 1962)

| | Inv(a+ b−) | Inv(a+ b+) | Inv(a− b+) | Inv(a− b−) | Total |
|---|---|---|---|---|---|
| No. | 22 | 74 | 69 | 0 | 165 |
| % | 13.3 | 44.9 | 41.8 | – | 100.0 |

Gm(x), while Ropartz, Rivat, Rousseau and Lenoir (1961) tested 109 Japanese for Gm(a), Gm(b), Gm(x), Gm-like and Inv(a); all were Gm-like(−). Ottensooser, and Ropartz, Rivat, Rousseau and Lenoir (1961) also found all Japanese to be Gm(a+). Yokoyama and Ueno (1961) reported that 1.9 per cent of 952 Japanese were Gm(a−). Ropartz et al. (1961) point out that this percentage corresponds to the frequency of sera which in their experiment agglutinated the coated cells and suggest that this is what occurred in Yokoyama and Ueno's experiment. Since the latter did not run controls, this explanation seems reasonable.

Ottensooser found 22.4 per cent of the Japanese Gm(b+) and 43.1 per cent Gm(x+), while Ropartz, Rivat, Rousseau and Lenoir (1961) found 19.2 per cent Gm(b+), 34.8 per cent Gm(x+) and 50.4 per cent to be Inv(a+). In a study of another 270 Japanese Ropartz et al. (1961) found 47.8 per cent Inv(a+). The Japanese, like the Chinese, have alleles $Gm^{ab}$, $Gm^{a}$, and $Gm^{ax}$. Steinberg, Lai, Vos, Singh and Lim (1961), using Ottensooser's and Ropartz et al.'s data, have estimated the frequencies of these alleles to be .108, .681 and .211, respectively. It is clear that the three alleles occur with markedly different frequencies in the Chinese and Japanese.

Tests of 109 Alaskan Indians, of 34 South American Indians and of 50 Alaskan Eskimos for Gm(a), Gm(b), Gm(x) and Gm-like (Steinberg, Lai, Vos, Singh and Lim, 1961) indicate that these populations all have the alleles $Gm^{ab}$, $Gm^{a}$ and $Gm^{ax}$ as do the Chinese and Japanese. The estimated frequencies of these alleles among the Alaskan Indians were .009, .787 and .204, respectively, i.e., similar to the frequencies among the Japanese. The sample sizes for the South American Indians and the Eskimos are too small for meaningful estimates to be made.

It appears from the foregoing data that Caucasoid populations are characterized by alleles $Gm^{a}$, $Gm^{b}$ and $Gm^{ax}$, and the absence of Gm-like; Negroid populations by allele $Gm^{ab}$, the absence of Gm(x), and the presence of Gm-like; Mongoloid populations by alleles $Gm^{ab}$, $Gm^{a}$ and $Gm^{ax}$ and the absence of Gm-like.

The Australian Aborigines from the Western Desert region seem to be unique in that in them alleles producing Gm(b) are absent or very rare. This is not true of the Aborigines from the coastal region (Steinberg, Vos and Kirk, unpublished). The Desert Aborigines appear, on the basis of a sample of about 300, to have alleles $Gm^{a}$ and $Gm^{ax}$ only, while those from the coastal region appear (also on a sample of about 300) to have $Gm^{ab}$, $Gm^{a}$ and $Gm^{ax}$, i.e., those present in the Mongoloid populations.

The Inv(a) and Inv(b) alleles have been observed in all populations thus far studied. Inv(a) appears to have the lowest frequency in Caucasoids.