The Theories Of The Inheritance Of The Iso-Agglutinogens In The Blood

John McDonald
Carroll College

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THE THEORIES OF THE INHERITANCE OF THE ISO-AGGLUTINOGENS IN THE BLOOD

Submitted in Partial fulfillment of the requirements for the degree of Bachelor of Science in the department of Natural Science, Carroll College, Helena, Montana

May Twenty-Eighth, Nineteen Hundred Thirty-Three
THE THEORIES OF THE INHERITANCE OF THE ISO-AGGLUTINOGENS IN
THE BLOOD

There has been of late a great deal of interest in and investigation of blood grouping from a genetic standpoint. It is the purpose of this paper to give and discuss the present status of the theories regarding the inheritance of these agglutinating factors.

Dr. Karl Landstiner, a native of Austria, born in Vienna where he carried on the original research work in relation to blood grouping, but now an attache of the Rockefeller Institute for Medical Research, was first to recognize serological differences in human blood. In 1901 he found that twenty-two individuals whose blood he had examined could be divided into three distinct groups or types.

When the serum of one normal, healthy person and the red blood cells of another are mixed, instead of mixing freely the red blood cells often clump or glue together. This phenomenon of clumping or gluing together is termed iso-agglutination or agglutination.

Iso-agglutination does not take place at random but depends upon certain definite properties of the blood. It is on the basis of these properties that blood was divided into separate groups. Three of the four general groups are attributed to Landstiner; the discovery of the fourth goes to the credit of two of his students.

Every human being belongs to one of the four general
groups and these groups are believed to be inherited according to Mendelian laws of heredity. If the blood group of each parent is known, in all probability one may state to what group their offspring might belong.

Another important factor in regards to these blood groups is that involving the technic of blood therapy. It is exceedingly important to match the blood of the donor to that of the recipient's for if the blood of the donor should happen to be a group that agglutinates the red blood cells of the recipient death is most likely to result.

It is a simple test to ascertain to what group an unknown blood belongs. To find out what group an unknown blood belongs a sample of the unknown blood is matched with the serum of the known groups A and B. The reading of the test depends upon whether clumping is manifested or not and may be read either microscopically or macroscopically.
Dr. Karl Landstiner, an attache of the Rockefeller Institute for Medical Research was awarded the Nobel prize for Medicine in 1930. He received this award for his masterful research work in Immunology. Among the first of Landstiner's discoveries was the group differences of human blood.

About 1900 Landstiner was investigating the agglutinating and lytic action of various sera to test whether individuals like species were serologically recognizable. By 1901 he had enough data to substantiate a biological conception of individual differences in blood. In that year he published an account of three blood groups and correctly recognized the existence of two major agglutinogens in the red blood cells and the two agglutinins in the sera which constitute the basis of this type of serological differentiation of individuals. At the same time he pointed out the significance of iso-agglutination for blood transfusions.

In 1902, two of Landstiner's students, Sturli and Descastello, continuing the work described the fourth blood group. Since the discovery of these agglutinating factors in human blood, blood grouping has come to be looked upon as being of great importance both in blood therapy and Forensic Medicine. Blewett, of the New York City Bar Association writes, "With the knowledge already at hand, based largely on the extensive investigations of the subject of transfusion of the blood, in about one-fourth of
the cases blood tests can determine, so surely that no self-respecting court could refuse to accept the proof, that a given man could not possibly have been the father of a certain child.*

The above quotation presents the problem of this paper. To show that the blood groups are inheritable and to discuss the theories concerning as to how these blood groups are inherited. Now Landstiner showed that there are two agglutinable substances, commonly designated A and B in the corpuscles. The presence or absence of these two substances determines the blood groups. Jansky and Moss has given us a means of classification, but there is some confusion in there classifications because they used the same means of symbolizing there classifications, namely, that of numbers. Today the serologist is coming to use letters to designate the groups. Below is a table to show the different classifications.

<table>
<thead>
<tr>
<th>Systems of classifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letter</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>AO</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>AB</td>
</tr>
</tbody>
</table>

The following is the reading of this table: the serum of an individual will agglutinate whichever one of the two substances, A or B, his own cells do not contain. Thus serum of Group A will agglutinate the corpuscles of Group B and 0 and serum of Group 0 fails to agglutinate any of the other groups because it contains neither A or B. Thus it is known as the "Universal" and may be used generally in blood

transfusions without any harmful effects.

Every individual retains his particular blood characteristic throughout life. Furthermore, as shown by von Dungren and Hirschfeld, in 1910, the blood groups are hereditary according to the Mendelian laws. They are not, however, present in the child at birth. "According to recent studies by Unger, only about 25 per cent of newborn children have cells that can be agglutinated. And only about 13 per cent of newborn children have iso-agglutinins. Incompatibility may occur between mother and child."

Two genetic theories have been proposed to account for the inheritance of the human blood groups. The two-factor hypothesis was first suggested; being propounded by von Dungren and Hirschfeld in 1910, it assumes that the agglutinogen A is brought out by the dominant phase of one pair of alleomorphs while B is brought out by the dominant phase of an independent pair.

Thus if one pair of genes be represented by A and a and the other by B and b then Group O must necessarily be of genotype aabb; Group A might either be AAbb or Aabb; Group B aaBB or aaBb; and Group AB, AAbb, AABb, AaBb, or AaBB. An individual of genetic constitution AaBb mated to one of similar constitution would yield the characteristic four phenotypes (like the four blood groups) in the familiar 9:3:3:1 ratio of the ordinary Mendelian dihybrid.

Bernstein suggested the theory of triple alleomorphs in 1925. It assumes that the genes for the agglutinogens A and B are dominant as in the case of the two-factor hypothesis but alleomorphs with a common recessive phase.

* Zinsser, Hans: "TEXTBOOK OF BACTERIOLOGY", 1931
Furuhata also proposed a theory which gives the same expectations as does Bernstein's theory of triple alleomorphs, but as stated it is one of two pairs of factors completely linked. Like Bernstein's theory it too was proposed in 1925.

If for the two-factor hypothesis the genes for the absence and presence of the isoagglutinogen A be represented by the symbols a and A and the genes for the absence or presence of the isoagglutinogen B by b and B; and for the theory of triple alleomorphs the genes for the isoagglutinogen A and B represented by IA and IB, respectively, and their common recessive phase by r, the four blood groups according to the two theories will be represented by the phenotypes and genotypes as given in the following table.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Two-factor hypothesis</th>
<th>Triple alleomorphs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phenotypes</td>
<td>Genotypes</td>
</tr>
<tr>
<td>O</td>
<td>aabb</td>
<td>aabb</td>
</tr>
<tr>
<td>A</td>
<td>A-bb</td>
<td>AAbb, Aabb</td>
</tr>
<tr>
<td>B</td>
<td>aaB-</td>
<td>aaBB, aaBb</td>
</tr>
<tr>
<td>AB</td>
<td>A-B-</td>
<td>AAbb, AaBB</td>
</tr>
</tbody>
</table>

Zinsser writes concerning Bernstein's conception of triple alleomorphs: "Bernstein, whose views are thoroughly analyzed by Hirschfeld's extensive article, suggests that instead of there being two sets of alleomorphs, A and alpha, B and beta, the hereditary principles depend upon three alleomorph genes, a recessive, R and two dominants, A and B. According to this conception the genetic formulae of the groups are as depicted in the following table, which is taken from Hirschfeld.
"It is relatively simple, if Landstiner's conception of the condition is correct, to forecast from the genetic formula the various combinations which are possible when individuals of two different groups mate. It is conversely also possible in a limited number of cases to state definitely that two given individuals cannot have children of certain groups. The following table, also taken from the article of Ottenberg and Beres, illustrates this condition.

<table>
<thead>
<tr>
<th>Group</th>
<th>Genetic formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>RR</td>
</tr>
<tr>
<td>A</td>
<td>AA</td>
</tr>
<tr>
<td>B</td>
<td>BB</td>
</tr>
<tr>
<td>AB</td>
<td>AB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parents</th>
<th>Children possible</th>
<th>Children not possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 x 0</td>
<td>0</td>
<td>A, B, AB</td>
</tr>
<tr>
<td>0 x A</td>
<td>0, A</td>
<td>A, B, AB</td>
</tr>
<tr>
<td>0 x B</td>
<td>0, B</td>
<td>B, AB</td>
</tr>
<tr>
<td>A x A</td>
<td>0, A</td>
<td>B, AB</td>
</tr>
<tr>
<td>A x B</td>
<td>0, A, B, AB</td>
<td></td>
</tr>
<tr>
<td>A x AB</td>
<td>0, A, B, AB</td>
<td></td>
</tr>
<tr>
<td>B x B</td>
<td>0, B</td>
<td></td>
</tr>
<tr>
<td>B x AB</td>
<td>0, A, B, AB</td>
<td></td>
</tr>
<tr>
<td>AB x AB</td>
<td>0, A, B, AB</td>
<td></td>
</tr>
<tr>
<td>0 x AB</td>
<td>0, A, B, AB</td>
<td></td>
</tr>
</tbody>
</table>

"A amount of information can be obtained from these data in medico-legal situations in which parentage and illegitimacy are involved. Ottenberg has given this matter considerable attention, as have a number of others, and in spite of the rare exceptions to the rules discussed which have been found from time to time, it seems justified to state in certain cases that a given child could not have been the offspring of a particular father. Hooker and Boyd have done a very useful piece of work in calculating the
the probabilities of determining non-paternity in given cases. Basing their calculations upon the frequency distribution of the blood groups among the white population of the United States, the probabilities of proving non-paternity when the blood groups of the accused man is known are as follows:

<table>
<thead>
<tr>
<th>Group</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 in 5</td>
</tr>
<tr>
<td>A</td>
<td>1 in 17</td>
</tr>
<tr>
<td>B</td>
<td>1 in 7</td>
</tr>
<tr>
<td>AB</td>
<td>1 in 2</td>
</tr>
</tbody>
</table>

The two proposed theories might be tested on a basis of mating results. The expectations from mating of parents restricted to groups, 0, A and B are identical for the two theories, but they differ, as shown in the table below, when one or both of the parents are of the rather uncommon AB group. From these matings the expectations are more limited under the theory of triple alleomorphs.

<table>
<thead>
<tr>
<th>Mating</th>
<th>On the basis of a two-factor hypothesis may give children of group</th>
<th>On the basis of a theory of triple alleomorphs may give children group</th>
</tr>
</thead>
<tbody>
<tr>
<td>O x AB</td>
<td>O, A, B, AB</td>
<td>A, B</td>
</tr>
<tr>
<td>A x AB</td>
<td>O, A, B, AB</td>
<td>A, B, AB</td>
</tr>
<tr>
<td>B x AB</td>
<td>O, A, B, AB</td>
<td>A, B, AB</td>
</tr>
<tr>
<td>AB x AB</td>
<td>O, A, B, AB</td>
<td>A, B, AB</td>
</tr>
</tbody>
</table>

The data which have been collected by different investigators from critical matings include children of all four groups as expected under the two-factor hypothesis and therefore include exceptions to the theory of triple alleomorphs. However, the number of children of group 0 and of group AB from O x AB matings and of 0 children from the other critical matings is so greatly in defect of expectations under the two-factor hypothesis as to point rather to a

*Zinsser, Hans; "Resistance to Infectious Diseases," 283-84
theory of triple alleomorphs. Under the latter view the exceptions are interpreted as due to illegitimacy or to errors of technic. The alternative suggestion, made recently by Bauer, that the small number of children of certain groups under the two-factor hypothesis may be due to a partial linkage of the factors.

Another method of testing the two theories that seems better or at least well suited to the case in question is one that is based on a comparison of observed blood group frequencies and frequencies expected on the basis of the two theories. It seems especially well suited, because there are in the literature, the observed group frequencies of a large number of populations from various localities and of various races of people, and the frequencies expected on the basis of the two theories are readily calculated.

Strandskov studied the blood group frequencies of 67 populations, tested according to the above method. The observed group frequencies are taken from the literature; the frequencies expected on the basis of the two theories are calculated according to the formulae given below.

As previously mentioned the two-factor hypothesis involves two independent pairs of alleomorphs. It is well known that any pair of alleomorphs in a population bred at random gives three genotypes, and that the frequencies of the three reach and indefinitely remain in equilibrium in the proportions of a binomial square. Thus if a pair of alleomorphs (a and A) is present in the proportions s and 1-s, the three possible genotypes will be present in the proportions
s^2:2s(l-s):(1-s)^2; and the phenotypes aa and A- will be present in the proportions s^2:1-s^2. Two pairs of genes present in the same population will, even if linked, tend more or less rapidly to reach and remain in equilibrium in proportions given by the product of their binomial squares. Thus assuming as above that the genes a and A are present in a population in the proportions s and 1-s, and assuming that the genes b and B, are present in the proportions t and 1-t, the four genotypes aabb, A-bb, aaB-, and A-B- will reach and remain in the equilibrium proportions s^2 t^2:(1-s^2)t^2: s^2(1-t^2):(1-s^2)(1-t^2), respectively.

If the two series are linked as under Bauer's hypothesis and do not combine at random initially, random combination is approached in direct proportion to the mean percentage of crossing over of the two sexes. (Robbins.) With 50 per cent crossing over or random assortment, the departure from random combination is halved in each generation. With 10 per cent crossing there is a 10 per cent approach to random combination from which it can be shown that it requires 6.6 generations to halve the initial departure. The proportions thus should come rapidly to equilibrium after race mixture even though there is a close linkage.

By making use of the relations outlined above it is possible to obtain from observed blood frequencies estimates of s^2 and t^2, and from these it is possible to calculate frequencies expected on the basis of the two-factor hypothesis. An example of the calculations involved is given.

The observed Javanese percentage frequencies of groups
0, A, B, and AB are 39.9, 25.7, 29.0, and 5.4, respectively.* It is evident that \( s^2 \) equals \( s^2t^2 + s^2(1-t^2) \) and, therefore, from the above relations \( s^2 \) equals the percentage frequency of groups O and B and in this case equals 39.9 + 29.0 or 68.9. It will also be evident that \( t^2 \) equals \( s^2t^2 + (1-s^2)t^2 \), or the sum of the observed percentage frequencies of groups O and A, in this case 39.9 + 25.7 or 65.6.

In obtaining estimates of \( s^2 \) and \( t^2 \), estimates of \( 1-s^2 \) and \( 1-t^2 \) are given at once. From these four values, estimates of the percentage frequencies of the four groups may be obtained by multiplication. In this particular case \( 1-s^2 \) equals 1-68.9 or 31.1, and \( 1-t^2 \) equals 1-65.6 or 34.4.

Three alleomorphs in a population bred at random are known to form genotypes with frequencies given by the square of the trinomial representing their frequencies. Thus if the alleomorphs \( I^A \), \( I^B \) and \( \tau \) are present in a population in the proportions \( x \), \( y \), and \( z \), respectively, the frequencies of the genotypes will be given by \( (x + y + z)^2 \), and the four phenotypes \( rr \), \( I^A \tau \), \( I^B \tau \), and \( I^A I^B \) will have the proportions \( z^2: x^2 + 2xz: y^2 + 2yz: 2xy \), respectively.

Employing the above relations it is possible to obtain estimates of \( x \), \( y \), and \( z \) from the observed blood group frequencies, and from these estimates it is possible to calculate frequencies expected on the basis of a theory of triple alleomorphs. An example follows.

The observed Javanese percentage frequencies are 39.9, 25.7, 29.0, and 5.4. Letting the sum of the frequencies \( x \), \( y \), and \( z \) equal one, \( x \) equals \( 1 + \sqrt{\frac{92}{2} + 2yz + y^2} \) and an estimate

--- Ichida, K.; "Jour. Immunol.", 1929, 16:92 ---
of $x$ equals $1 - \sqrt{0 + B}$ or 16.99. Similarly, $y$ equals $1 - \sqrt{2x + z^2 + x}$, and an estimate of $y$ equals $1 - \sqrt{0 + A}$ or 19.01. Having obtained estimates of $x$ and $y$, an estimate of $z$ is obtained by subtracting the sum of $x$ and $y$ from one; $z$ equals $1 - x - y$; in the present case $1 - 16.99 - 19.01$ or 64.00. From these estimates of $x$, $y$, and $z$ the expected frequencies according to the theory of triple alleomorphs are obtained by multiplication and addition.

Having calculated expected group percentages on the basis of the two theories it would be possible from a direct comparison of these and observed frequencies to formulate an opinion as to the relative goodness of fit of the two theories but an exact test of agreement is desirable. Pearson's well known $X^2$ test seems appropriate. It gives values from which may be obtained the probability that random sampling from calculated system of frequencies could lead to as divergent a system of frequencies as that observed.

The ordinary formula for the determination of $X^2$ is

$$X^2 = \sum \frac{(O - C)^2}{C}$$

where $O$ and $C$ are the observed and calculated frequencies respectively. It will be convenient here, however, to use observed and calculated percentages instead of absolute numbers. Thus letting $O$ and $C$ stand for percentage frequencies, and $N$ for the total number of individuals tested, the formula becomes,

$$X^2 = \frac{N}{100} \sum \frac{(O - C)^2}{C}$$
The observed Javanese percentage of groups 0, A, B, and AB are 39.9, 25.7, 29.0, and 5.4, respectively. The expected percentages calculated on the basis of a two-factor hypothesis are 45.2, 20.4, 23.7, and 10.7, respectively. \( \chi^2 \) for all four frequencies equals 5.3, \( (O - E)^2 \) equals 28.09, \( \chi^2 \) equals 1346. Employing the above formula, \( \chi^2 \) for the Javanese, on the basis of a two-factor hypothesis, equals

\[
\frac{1346}{100} \left( \frac{28.09}{45.2} + \frac{28.09}{23.7} + \frac{28.09}{10.7} \right) = 79.265
\]

On the basis of the theory of triple alleomorphs \( \chi^2 \) for the Javanese has a value of 4.150.

Having calculated \( \chi^2 \), the probability that random sampling will give as great a deviation from data in which the theory holds may be obtained from prepared tables. (c. f. Jour. Immunol. p. 92)

The conclusion is reached that the theory of triple alleomorphs explains better the inheritance of human blood groups than does the two-factor hypothesis of von Dungern and Hirschfeld, whether or not it is assumed that the factors of the latter are linked. I fully believe that I have presented sufficient data to warrant this conclusion, and the facts gathered on the matter demands that I draw the above conclusion.
THE THEORIES OF THE INHERITANCE OF THE ISO-AGGLUTINOCENS IN THE BLOOD

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McDonald John Patrick

Birthplace: Anaconda City
Date Oct. 14, 1906.

Montana State

Grammar schools attended:
St. Helena's Cathedral Parish School........... 1912-1915.
Lewis and Clark rural school, Dist. # 16..... 1915-1918.

Academy attended:
Mount St. Charles Academy..................... 1926-1929.

College attended:
Carroll College............................... 1929-1933.