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Hereditary influence of blood group factors on the population problem

Tanemoto Furuhata (Japan)

Summary

There are various blood groups, types and subtypes as ABO, MN, Q-q, E-e, S-T (secretor and non-secretor), I-i, J-j and Rh-Hr. Considerable progress has been made in Japan in the study of these groups. The blood group factors are all inherited and since, according to the manner of mating, they may be the cause of intra-uterine selection of habitual abortion of the foetus or of erythroblastosis foetalis. They have an intimate relation to the population problem.

When the female parent does not have the factor and the male parent has, in most cases it is transmitted to their child. In instances of this type the blood group factor of the foetus often enters the blood system of the mother and isoimmunizes her by producing an antibody. This antibody contrariwisely enters the foetus, destroys its blood cells, disturbs its growth and finally produces abortion. Even though the delivery may take place, death due to erythroblastosis foetalis can occur.

As the cause of foetal death the action of the blood group must not be overlooked.

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* General distribution of this document is limited to the introductory summary. Participants who have been invited to take part in the meeting referred to above will receive also the full text of the paper. Other participants in the Conference will receive the full text upon request.

Pour la traduction française voir au verso.

Influence héréditaire des facteurs sanguins sur le problème de la population

Tanemoto Furuhata (Japon)

Résumé. On peut classer le sang en divers groupes, types et sous-types, tels que ABO, MN, Q-q, E-e, S-T (secréteur et non secréteur), I-i, J-j et Rh-Hr. Des progrès considérables ont été réalisés au Japon dans l'étude de ces groupes. Les facteurs sanguins sont tous héréditaires; ils peuvent donc selon le mode d'union des individus être la cause d'une sélection intra-utérine, d'avortements répétés du foetus ou l'erythroblastose du foetus. Ces facteurs sont intimement liés au problème de la population.

Lorsque la mère ne possède pas un facteur et que le père le possède, ce facteur peut être transmis à l'enfant issu de leur union. Dans de tels cas, le facteur sanguin du foetus pénètre souvent dans le système sanguin de la mère et l'immunise en secrétant un anticorps. Cet anticorps, par un processus inverse, pénètre dans le foetus, en détruit les globules sanguins, gêne sa croissance et finalement entraîne l'avortement. Même si l'accouchement est possible, il peut en résulter la mort du foetus par erythroblastose du foetus.

Il convient de ne pas négliger l'action du groupe sanguin comme cause de la mort du foetus.

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* Seule la présente analyse d'introduction fait l'objet d'une distribution générale. Les participants qui ont été invités à assister à la séance mentionnée recevront en outre le texte intégral du document. Les autres participants au Congrès recevront le texte intégral sur leur demande.

Hereditary Influence of Blood Group Factors on the Population Problem

E/CONF.13/41
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ORIGINAL:
ENGLISH

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(1) Introduction.

There are various blood groups, types and subtypes as ABO, MN, Q-q, E-e, S-T (secretor and non-secretor), I-i, J-j and Rh-Hr, some have been studied in Japan remarkable progress being made. The blood group factors are all inherited and since, according to the manner of mating, they may be the cause of the intrauterine selection of habitual abortion of the fetus or of erythroblastosis fetalis, they have an intimate relation to the population problem.

The author wishes to present here principally the data made clear in Japan.

(2) Partial Antigens and Partial Antibodies.

(a) Analysis of B group substance.

The B group substance was analyzed into three partial antigens by S. MIZUTANI (1932), T. YAMAZAKI (1932-33) and FRIDENREICH and WITH (1933). These are called B_I, B_{II} and B_{III}, respectively, in Japan. Against these partial antigens there are the respective partial antibodies, anti-B_I, anti-B_{II} and anti-B_{III}.

Table 1

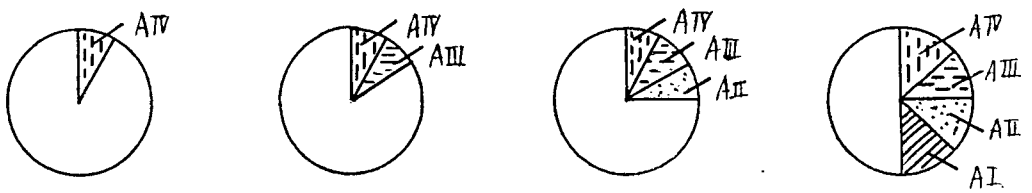
Classification of B Group Substance

S. MIZUTANI (1932)	B_4	B_3	B_1	B_2
T. YAMAZAKI (1932-33)	B_1	B_4 — B_2 — B_3		B_5
FRIEDENREICH & WITH (1933)	B_1	B_2	B_3	-
T. FURUHATA (1935)	B_I	B_{II}	B_{III}	C

(b) Analysis of A group substance.

M. TERAJIMA (1942) analyzed the A group substance into the partial antigens, A_I, A_{II}, A_{III} and A_{IV}. He named A_I the human part, A_{II} the dog part, A_{III} the pig part and A_{IV} the sheep part. According to him the human A blood cell has the structure ($A_I \cdot A_{II} \cdot A_{III} \cdot A_{IV}$), the dog A blood cell ($A_I \cdot A_{II} \cdot A_{III}$), the pig A blood cell ($A_{III} \cdot A_{IV}$) and the sheep A blood cell (A_{IV}). A_{IV} is identical with SCHIFF and ADELSBERGER's antigen or SCHIFF's sheep part and THOMSEN's F_A. ISEKI and TERAJIMA (1942) made it clear that FORSSMAN's antigen is composed of ($F + A_{IV}$). The A group blood cells of sheep, pig, dog and human have the following structure:

1. Sheep 2. Pig 3. Dog 4. Human



The partial antigens produce the partial antibodies, anti-A_I, anti-A_{II}, anti-A_{III} and anti-A_{IV}.

(c) Analysis of C group substance.

HOOKER and ANDERSON (1921), DÖLTER (1925), OKABE (1928), MIZUTANI (1932), YAMAZAKI (1933), ASAKAWA (1933), OKAWA and NEKAWA (1934), KAGAYAMA (1935) and SHIBUYA (1936) observed that there is an antigen common to both the A and B group blood cells, but M. HIBINO (1935) made clear the existence of this antigen and called it C. C. KOBAYASHI (1942) subsequently analyzed the C antigen into the partial antigens, C_I, C_{II} and C_{III}.

TERAJIMA succeeded in discovering the anti-C agglutinin and the anti-C precipitin in the pig serum and UYEYAMA the anti-C agglutinin in the serum of fowl and rabbit. Thus, it became clear that the anti-

C agglutinin and anti-C precipitin are present in the normal animal serum and S. ISEKI and C. KOBAYASHI (1942) found the anti-C agglutinin in human serum of the O group. They examined 56 cases of O group human serum and obtained the following results:

Table 2

Frequency of Anti-C Agglutinin in Human O Serum

Kind of agglutinin	Number of cases	%
Anti-A + (anti-B_{II}+anti-B_{III})	30	53.6
Anti-A + (anti-B_{I}+anti-B_{II}+anti-B_{III})	14	25.0
Anti-A + (anti-B_{II}+anti-B_{III})+ anti-C	12	21.4
Total	56	100.0

Anti-C agglutinin is observed in 21.4% of O group serum.

(d) Analysis of O substance.

O substance is contained in all types of human blood cells and in the animal blood cells. O substance is analyzed into the partial antigens, O_I, O_{II} and O_{III}. O_I, O_{II} and O_{III} produce the respective partial antibodies, anti-O_I, anti-O_{II} and anti-O_{III}.

(e) Chemical properties of the group substance.

In regard to the chemical properties of the blood group substance there are many opinions, but none are definite. Some state it is of protein nature and others of polysaccharide nature and still others of lipoid nature.

By our study the blood group substance is found in the three fractions of protein (p), lipoid (l) and polysaccharide (k). In other words the A substance is composed of ($A^l + A^p + A^k$), the B substance of ($B^l + B^p + B^k$), the C substance of ($C^l + C^p + C^k$) and the O substance of ($O^l + O^p + O^k$).

However, the blood group substance contained in the saliva and gastric juice is found mainly in the carbohydrate fraction and that in the body of the bacillus is found mainly in the lipoid fraction. I consider that the group substance is probably composed of a mosaic structure of lipoid, polysaccharide and protein. The partial antigens in these fractions produce the respective antibodies, as anti-A^l, anti-A^k and anti-A^p.

(3) M-N Blood Type.

The M-N blood types were discovered by Landsteiner and Levine (1927-28). However, at the time of discovery, it was reported that the anti-M and anti-N could not be observed in the normal serum and the M and N antigens were proven only by the immune serum, whereas S. ISEKI and T. FUKAO (1936) discovered the anti-N agglutinin in the normal rabbit serum. The following year ISEKI, FUKAO and J. SUZUKI (1937) discovered the anti-N agglutinin in the normal human serum and J. SUZUKI (1937) the anti-M and anti-N agglutinins in the pig serum. H. IIJIMA and S. IMAMURA (1937) discovered the anti-M agglutinin in the normal human serum. D. TANIGUCHI, K. YOSHIKAWA and T. KOSHINO (1937) discovered the anti-M and anti-N agglutinins in the sera of the rabbit and pig and C. HAEBARA (1937) the anti-M and anti-N agglutinins in the sera of the rabbit and goat, the anti-N agglutinin in the Formosan monkey serum, the anti-M agglutinin in the buffalo serum and the anti-N agglutinin in the pig serum. S. TOKUNAGA (1940) discovered the anti-N agglutinin in the snapping turtle serum. Thus, it became clear that the anti-M and anti-N agglutinin are contained in the normal serum of the human being and other animals.

(a) Subgroup of M.

S. HAYASHIDA (1944) and T. TOKUGAWA (1945) discovered that there

are the subgroups, M_1 and M_2 in M. HAYASHIDA learning that M is present in the blood cell of the Formosan monkey (Macacus cyclopis) found that by absorbing many anti-M sera with monkey blood cells there are sera which are easily absorbed by the monkey blood cell and those which are not. The M of the monkey blood cell is more simple in structure than that of the M of the human blood cell. If we call this M_2, there are the M_1 and M_2 types in the M of human. M_1 is hereditarily more dominant than M_2. Therefore, genetically they can be classified into the three genotypes of M_1M_1, M_1M_2 and M_2M_2.

HAYASHIDA examined 1350 persons (935 males and 415 females) and obtained the following results:

M_1	1037	(84.2%)
M_2	213	(15.8%)

Of the 81 sets of monozygotic twins 75 sets (92.6%) were M_1 and 6 sets (7.4%) M_2; of the 56 sets of dizygotic twins 23 sets (41.1%) were M_1, 5 sets (8.9%) M_2 and the remaining 28 sets were of different MN blood groups.

(b) Subgroups of N.

M. TANAKA (1950) discovered that in the N type some blood show a strong ability to agglutinated and others a weak agglutination. If we call the former N_1 and the latter N_2, 92.3% are N_1 type and 7.7% N_2 type, and N_1 is more dominant hereditarily than N_2.

(4) Q-q Blood type.

While studying the serum types of pig serum S. IMAMURA (1934) discovered that there was a specific agglutinin present in No. 225 pig serum. In reviewing the literature he found that it was similar to the anti-P of Landsteiner and Levine (1928). Anti-P serum, donated by Landsteiner, was compared with his new agglutinin, and the two were

found to be distinctly different from each other. He named this agglutinin the anti-Q agglutinin and called the blood cell that is agglutinated by this agglutinin the Q type and the blood cell that is not agglutinated the q type.

Distinction Between Q and P of Landsteiner and Levine.

The anti-P donated by Landsteiner was the B group human serum. In this serum was contained the anti-A agglutinin. Therefore, excluding the A group blood cell, comparison was made between the B group and O group blood cells. (Table 3)

Table 3

Anti-P (Landsteiner & Levine)		Anti-Q	Number of Cases	%
1)	+	−	7	18.4
2)	−	+	4	10.4
3)	+	−	16	42.1
4)	−	+	11	29.0

At 0°C. anti-P showed a stronger agglutination reaction than at 20°C.and 30°C. On the other hand, the anti-Q serum reacted stronger at 20°-25°C. than at 0°C.; at 30°C. the reaction became weak, and disappeared at 37°C.

While this experiment showed that the anti-P and anti-Q are very much alike, it clearly indicated that they are different substances.

Q is present in 32% of the Japanese population and q in 68%. The anti-Q agglutinin can be observed in 3% of pig sera and ISEKI and FUKAO (1936) and AKAI (1939) discovered it in the rabbit serum, KIKKAWA (1937) in the fowl serum, SUZUKI (1937), AIDA (1937), SEKIYA (1939) and WATANABE (1942) in the pig serum and SUZUKI (1937) in the human colostrum and human serum.

SUZUKI observed an anti-Q agglutinin with a titer of 1:256 in the colostrum of a woman in the Red Cross Hospital in the city of Kanazawa, and, when the serum of this woman was examined, a high titer anti-Q was discovered. Thinking that certainly the anti-Q agglutinin is always present in the human serum, SUZUKI examined the various types of sera in 1391 persons and discovered the anti-Q agglutinin in 42 persons (3 %).

SUZUKI examined 122 children of 47 families and reported that the anti-Q agglutinin inherits recessively. Later, FURUHATA and IMAMURA (1947) examined 133 children of 43 families and arrived at the same conclusion as SUZUKI. By the results of a survey of 100 families E. MATSUNAGA (1949) confirmed the recessive hereditary character of the anti-Q agglutinin. The anti-Q agglutinin cannot be found in the Q type person but can be found in the q type. If we call the person having the anti-Q agglutinin q+ and the one without it q−, the heredity of q+ is of a recessive type as compared to that of q−. I. KANEDA (1951) divided the Q type into the subgroups, Q_1 and Q_2. The Q_1 is dominant to Q_2.

(5) E-e Type Blood Group.

The eel serum can be divided into types I, II and III. However, SUGISHITA (1935), using the type II eel serum, classified the A, B and AB blood groups into E and e types, but, he could not divide the O blood group into E and e types. M. MURAKAMI (1950), succeeded in classifying the O blood group into the subgroups, O_1 and O_2 types, and also was able to divide the O blood group into the E and e types.

(6) S-T Type (Secretor and Non-secretor).

SHIFF and SASAKI (1932) classified humans into secretors (S) and non-secretors according to the human saliva. Studies were made in

Japan on the production of group specific precipitin, through the application of "serum type" and "saliva type" and the principle of "intravital filtration." These workers produced anti-A precipitin, anti-B precipitin, anti-O precipitin and anti-C precipitin. Of course, besides these, various partial antibodies can also be produced. FUKAO (1936) first succeeded in producing the anti-A precipitin and anti-B precipitin, and after this K. KIKKAWA (1938) produced the anti-O precipitin.

On the basis of the anti-O precipitin the various types of salivas are divided easily into S and s types. R. UYEYAMA (1937) discovered in the normal fowl serum an anti-T precipitin which reacts only with the non-secretor type saliva and not with the secretor type saliva. In other words by using the anti-O and anti-T precipitins the secretor becomes the St type and the non-secretor the sT type. We call this the S-T type. Partial antigens A_I, A_{II}, A_{III} and A_{IV} are present in the saliva of the A group secretor, but A_I is absent from the saliva of the non-secretor and A_{II}, A_{III} and A_{IV} are present only in slight amounts. In the same manner, B_I, B_{II} and B_{III} are all present in the saliva of the B group secretor, but no B_I is present in the non-secretor and there are only small amounts of B_{II} and B_{III}. In the saliva of each type of secretor O_I, O_{II} and O_{III} are secreted but in the saliva of the non-secretor O_I is not secreted. The T substance is secreted in only the non-secretor and not in the secretor. The T substance is contained abundantly in the meconium of the newborn. Therefore, by immunizing the fowl with the saliva or the meconium of a non-secretor an immune anti-T precipitin can be produced.

(7) Rh-Hr Type.

Landsteiner and Wiener (1940) discovered the Rh factor and there-

after in America and England the study on the Rh factor has made great strides. Various English workers have reported C,D,E,c,d,e,C^w,C^u, c^v, E^u and D^u factors, and more recently, the factors Duffy, Lewis, Kell-Cellano, Lutheran, Levy and Jobbins have been discovered. Since this phase of the problem is well known in Europe and America, I need not discuss it further.

(8) I-i and J-j Types.

ISEKI and MAKINO (1950) discovered an antibody in the serum of a pregnant woman-and named this the anti-I agglutinin and the following year discovered a new antibody in the serum of another pregnant woman and named it the anti-J agglutinin. However, it is said that the anti-I and anti-J may be the same as anti-C and anti-Le^a, respectively. Recently, two new antibodies were discovered in the author's laboratory. At present the nature of these antibodies are being investigated and it is clear that both are the cause of erythroblastosis fetalis.

(9) Intrauterine Selection of Fetuses.

I made a brief description principally of the blood type factor studied in Japan but I wish to call attention to the fact that the greater part can be related to the death of the fetus.

There are many reports on the relation between the various Rh factors and erythroblastosis fetalis but as there are about 0.4-0.6% Rh- in Japan, erythroblastosis fetalis due to the action of the factor is rare in this country. However, many authors have reported recently that erythroblastosis fetalis occurs due to the incompatible mating of ABO types. E. MATSUNAGA (1952,1953) has made a detailed report on "Intra-uterine Selection by the ABO Incompatibility of Mother and Foetus". Moreover, there are several case reports on

habitual abortion due to the I and J factors discovered by ISEKI and MAKINO.

Conclusion

Many blood group factors are known to be present in human blood and it is probable that further research will reveal others.

Moreover, when the female parent does not have the factor and the male parent has, in most cases it is transmitted to their child. In instances of this type the blood group factor of the fetus often enters the blood stream of the mother and isoimmunizes her, by producing an antibody. This antibody contrariwisely enters the fetus, destroys its blood cells, disturbs its growth, and finally produces abortion. Even though the delivery may take place, death due to erythroblastosis fetalis can be happened.

As the cause of fetal death the action of the blood group must not be overlooked.