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INDIVIDUAL DIFFERENCES IN HUMAN BLOOD[1]

By KARL LANDSTEINER, M.D.

ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH

BECAUSE of the difficulties in working with substances of high molecular weight, one is as yet far from the goal of chemically characterizing the single proteins and determining the constitution of these substances, which rank as the most important components of living matter. Hence it was not the use of the ordinary chemical methods, but the application of serological reagents, which led to an important general discovery in protein chemistry, namely that the proteins in various animals and plants are different and are specific for each species. The multiformity is increased by the fact that also various organs contain particular proteins. It thus would appear that in the case of living organisms, special structural substances are required for each single form and function, in contrast to artificial machines, which, serving the most diverse purposes, may be constructed from a limited number of materials.

The discovery of biochemical species specificity prompted the question which formed the basis of the investigations about to be discussed, as to whether the specific differentiation goes beyond the limits of species, and whether also the individuals within a species show similar, though presumably slighter, differences. As no observations whatever were available pointing to such behavior, I chose the simplest amongst the possible plans of investigation, and that material which gave promise of useful application. Accordingly, the investigation consisted of allowing blood serum and red blood corpuscles of different human individuals to interact.

The results were only partially those that had been expected. In many tests, just as if the blood cells had been mixed with their own serum, no changes were

[1] Nobel Lecture read in German at Stockholm, December 11, 1930.

observed. Frequently, however, a phenomenon described as agglutination occurred, the serum causing a clumping of the cells of the other individual.

The unexpected feature was that the agglutination, when it did occur, was as marked as the well-known reactions in which serum and cells of different animal species interact, whereas in other cases there seemed to be no difference in the blood of various individuals. At this point it was still to be considered that the phenomena observed did not signify the individual differences sought for and that the reactions, though obtained with the blood of healthy individuals, might have been due to a past history of disease. It soon became evident, however, that the reactions followed a law which holds for the blood of all human beings, and that the properties observed are as characteristic for single individuals as are the serological properties distinguishing species. There are in the main four different kinds of human blood, constituting the so-called blood groups. The number of the groups depends on the existence in the erythrocytes of substances (isoagglutinogens) having two different structures, either or both of which may be present or absent in the erythrocytes of a given person. This alone would not be sufficient to explain the reactions; the active substances of sera, the isoagglutinins, must also occur in a definite distribution. Such is indeed the case, for every serum contains those agglutinins which act upon the agglutinogens not present in the cells, a remarkable phenomenon, the cause of which has not yet been definitely established. From these facts there follow definite relationships, shown in the table below, between the various blood groups, which make the task of their determination a simple one. The groups are designated according to the agglutinogens contained in the cells. (In the table the sign + indicates agglutination.)

Serum of group	Agglutinins in serum	Erythrocytes of group			
		O	A	B	AB
O	αβ	−	+	+	+
A	β	−	−	+	+
B	α	−	+	−	+
AB	−	−	−	−	−

The question will now be asked whether isoagglutination is limited to human blood, or occurs also in that of animals. As a matter of fact, such reactions are found among animals, but they are definite only in the case of certain species, and are hardly ever as consistent as in the case of man. Only the highest anthropoid apes—the blood cells of which are indeed distinguishable from those of man, the proteins as yet not definitely so—have blood group characteristics which, as far as has been investigated, are shown to coincide completely with those of man. It may be assumed that the comparative study of numerous animal species will serve to elucidate the phenomenon of group formation, which is not yet completely understood.

A noteworthy piece of work with respect to animal blood is already at hand. Very soon after the first observations on isoagglutination had been made, Ehrlich and Morgenroth described experiments in which they demonstrated variations in the blood of goats by the use of hemolytic antibodies—the isolysins—which were formed when the animals received injections of blood from other individuals of the same species. No typical blood groups were observed, but rather numerous apparently irregular differences, a finding which, apart perhaps from the intensity of the reactions, is about what might have been expected on *a priori* grounds. Similar investigations, particularly those of Todd on cattle and fowl,[2] pointed to almost complete individual specificity.

The apparent discrepancy between the observations made on man and the lower animals has recently been explained. Some suggestive observations having been reported previously, I was able, with Levine, to obtain definite results with the aid of special immune sera produced by injecting rabbits with human blood. This work led to the detection of three new agglutinable factors present in all four blood groups. Thus it could be established that there are at least 36 different types of human blood, if one also takes into account the subdivision of groups A and AB each into two subgroups,[3] which has been studied recently in my laboratory and thoroughly investigated by Thomsen. Furthermore, it could be demonstrated that iso-reactions of lesser intensity,[4] which do not follow the group rule and vary in their specificity, are more frequently found than was formerly supposed. As these irregular reactions can without difficulty be distinguished from the typical ones, they do not in the least invalidate the rule of the four blood groups. On the basis of these results we may assert that in the case of man there are numerous individual blood differences already demonstrated, and undoubtedly there exist still others which have not yet been established. Whether actually each individual blood possesses a special quality, or how frequently there is complete correspondence with the blood of others, can not be definitely stated at present.

These findings have, at the present time at least,

[2] Landsteiner and Miller, Todd.

[3] S. v. Dungern and Hirschfeld, Guthrie and collaborators.

[4] Unger, Guthrie and collaborators; Jones and Glynn; Landsteiner and Levine.

no special significance in the therapeutic application of the blood groups; they are, however, probably related closely to an important field of surgery, namely, that of the transplantation of tissues.

It has long been known that transplantation—for instance, of the skin—is much more successful when the transplanted tissue is that of the same individual, and this is also true of tumors transplanted to various strains of a species, as first described by Jensen. The experience of surgeons is confirmed by animal experiments, among which the important series of L. Loeb is especially noteworthy. His experiments consisted of the transplantation of different tissues—from the same individual, from those having blood relationship, from those not so related or belonging to different varieties and species. In general the success of transplantation stood in a reciprocal relation to the degree of consanguinity, and a review of all the findings permitted the conclusion that the tissues of a single individual must possess special biochemical properties.

The agreement between the results of the two independent methods is so striking that one is immediately led to assume that there are differences of substantially the same kind which, on the one hand, determine the individual variations detectable by means of serum reactions, and on the other, the individually specific behavior of transplants. As a support for the assumption it may be cited that the group characteristics, besides being present in the blood, can also be demonstrated in the cells of organs. On the basis of this theory, *i.e.*, taking into account the blood groups, it has been attempted to make tissue transplantation more successful; such efforts, however, have not led to consistent results. But this is understandable, for the blood groups constitute only a part of the existing serological differences, and even apparently slight deviations may influence the take of the transplant. Consequently, the difficulty that arises from the experiments may seem to be disposed of, and the most probable supposition would be that the two series of phenomena—the serological differences of the individuals and the transplantation specificity—are related in nature and depend on chemical differences of a similar sort. Hence there still remains a possibility that serum reactions may be employed in the future for the important problem of transplantation, although the knowledge available at present justifies no more than a hope in this direction.

Turning now to the question of the chemical nature of the substances underlying individual specificity, the answer, although almost wholly in the negative, is not without interest. The above-mentioned precipitin reactions, which revealed the species differences of proteins, were so impressive that the belief arose that proteins or related substances form the substrate of all serological reactions. This view was first disturbed by studies made on blood antigens. The solubility of specific substances in organic solvents, and particularly the investigations of the heterophile antigens of sheep blood, and organs of diverse animals discovered by the Swedish pathologist Forssman, which on extraction with alcohol yield a substance that is specifically binding but does not act as antigen, led me to the opinion that those parts of many cell antigens which determine their specificity are not albuminous substances, and that these fractions do not become antigenic until they are combined with proteins to form what may be conveniently called "complex antigens." A strong support for this view was found in the fact that it was possible by admixture with albuminous solutions to restore the antigenic power of the specific substance.[5]

Analogous results were obtained from the study of certain specific substances contained in bacteria (Zinsser). While for bacteria the chemical nature of the specific binding substances, or haptens, could be established with certainty—one deals in this case with colloidal polysaccharides (Avery and Heidelberger)—we do not yet possess definite information on the animal cell antigens. Nevertheless it may be stated that the biochemical characteristics of animal species are based on the existence of two diverse classes of species specific substances[6] which exhibit essential differences in the manner of their appearance.

What directly concerns our subject is the fact that group specific substances may also be extracted by alcohol from the blood corpuscles, and in general permit the formation of antibodies in this state only when mixed with antigenic proteins. We may, therefore, conclude that the haptens vary within a species, while analogous serological differences of proteins, although suspected, can not be definitely asserted. Another peculiarity is the fact that haptens which show relationships according to their reactions frequently are encountered in animal species widely separated in the zoological system. Thus isoagglutinogen A is serologically related to Forssman's antigen present in sheep blood, and for that reason certain immune sera react with sheep blood and with human blood of groups A and AB, but not with blood of groups O and B (Schiff and Adelsberger). Even more remarkable is the occurrence of similar structures in bacteria, which is shown by the presence of sheep lysins and apparently anti-A agglutinins in some antibacterial sera. This seems to be the case with

[5] Landsteiner and Simms.

[6] Landsteiner and Van der Scheer, Bordet and Renaux.

some anti-paratyphoid B immune sera, and a dysentery serum, recently described by Eisler, agglutinates human blood, and contains antibodies acting to a higher degree upon that one of the two subgroups of group A, which is less sensitive to the isoagglutinins.

The occurrence of isoantibodies showing individual differences is probably attributable, according to the results of investigations made on artificial complex antigens, to the fact that, through combination with other substances, proteins derived from the immunized species are capable of stimulating the formation of antibodies. If, on the other hand, haptens identical or closely related to those of the animal are injected in combination with foreign proteins, as a rule no antibodies are formed. As an example may be cited the experiments made by Witebsky, which demonstrated that group specific immune sera are formed after the injection of blood A only in the case of such rabbits whose organs do not contain substances similar to agglutinogen A. But that no definite rule can be set down is demonstrated by the experiments of Sachs and Klopstock on the appearance of the Wassermann reaction in rabbits after the injection of foreign serum mixed with alcoholic extracts of rabbit organs.

While in this instance the antibodies react only with organ extracts, O. Fischer, by injecting rabbit blood extracts mixed with foreign serum into rabbits, succeeded in producing autoantibodies which acted upon intact blood cells, and which were active hemolytically only after cooling, in a manner similar to the hemolysins which I, in collaboration with Donath, found to be the cause of hemolysis in paroxysmal hemoglobinuria. These results and the diversity of the immune sera produced with extracts of O and B red blood cells, and on the other hand with intact cells, point to the conclusion that the form of union of the substances within the cells also exerts an influence upon the antigen characteristics.

Following these brief remarks on individual blood differences and peculiarities of the cell antigens, we turn now to a discussion of the application of the group reactions. A voluminous literature, almost impossible of complete review, treating of the relative frequency of the individual blood groups among the various races of man, has come into existence since L. and H. Hirszfeld made the remarkable observation that in this respect there exist characteristic differences among the various races. Their most important finding was that the characteristic A is more frequently found among North Europeans than is the characteristic B, whereas the conditions are reversed among a number of Asiatic races. Another striking example is that the American Indians, when they are of pure race, belong almost exclusively to group O,[7] from which it is concluded that the occasional appearance of factors A and B is attributable to racial mixture.

To discuss the results of the anthropological investigations made on blood groups, and the conclusions derived therefrom, is beyond my province; the viewpoints of the various authors concerning the general principles and the individual problems are not in general accord. But there seems to be a prevailing belief that the behavior of the blood groups, in conjunction with other anthropological factors, may serve as an indicator of blood relationship and the descent of the races of man, and has, therefore, some anthropological significance.

A practical use of the group characteristics offered itself immediately for application in the differentiation of human blood stains for forensic purposes. With the aid of the precipitin reactions[8] it is not difficult to determine whether a certain blood stain is of human or of animal origin; but it was impossible for the forensic physicians to distinguish blood stains from various individuals. Since the isoagglutinins and the corresponding agglutinogens are preserved for some time in a dried state, the problem may be solved in certain cases, when the bloods to be examined—for instance, that of the accused person and that of the victim—belong to different blood groups. The occasions for employing the method are naturally not very frequent, and particularly in your country there is fortunately small opportunity for its use in this connection; but according to a report by Lattes, who was the first to apply the method in forensic practice, it has proved useful in a number of cases and has served as the basis for legal decision, sometimes as a criterion for establishing the innocence of the accused.

The group reactions have been employed far more extensively in forensic medicine in cases of disputed paternity. The possibility of making such decisions rests on the studies of the inheritance of the blood groups. The most important findings along this line we owe to v. Dungern and Hirschfeld. In their investigation they were able to determine that the two agglutinogens A and B are hereditary dominant properties, the inheritance of which follows the Mendelian law. The significance of this discovery lies in the fact that in the case of man there is hardly another physiological characteristic which can be so unequivocally demonstrated, and which at the same time follows so simple a rule. The genetic hypothesis of two independent pairs of genes, proposed by the above authors, had to be abandoned as the result of

[7] Coca, Snyder.
[8] Kraus, Bordet, Uhlenhuth.

the statistical work of Bernstein. On the basis of a definite gene hypothesis and on the premise of an adequate mixing of a certain population, it is possible to make calculations on the frequency of the inherited characters. A calculation of this kind was made by Bernstein, who found that the observed numbers and those calculated according to the hypothesis proposed by v. Dungern and Hirschfeld were widely divergent. On the other hand, there was complete agreement when the calculations were based on a hypothesis which postulates three allelomorphic genes in a certain locus of a chromosome. The assumption leads to definite expectations with respect to the children of AB parents, and these have been satisfied by the investigations of Thomsen, Schiff, Snyder, Furuhata and Wiener, with the exception of rare instances, which may possibly still be reconciled with Bernstein's theory. Hence the new theory has been almost universally accepted.

In forensic application, the dominance rule of factors A and B is standard. Hence paternity is excluded in all such cases in which a child is shown to possess A or B, when these characteristics are absent in the case of the mother and in that of the putative father. The test is quite frequently employed in several countries, particularly in Germany and Austria, and also in Scandinavia. In a review made last year by Schiff, he reports on about 5,000 forensic investigations, with 8 per cent. of excluded paternity, while according to a calculation there would be the possibility of such exclusions in 15 per cent. of the cases. In favor of the method it may be stated that it has also contributed to the recognition of illegitimate children by their fathers.

It may be of interest to indicate a further possible development in the decision of paternity. The preliminary results[9] obtained with two of the abovementioned blood properties demonstrated by immune sera point to the probability that their appearance is conditioned by a pair of genes, neither of which is dominant over the other, so that when both are present there results a mixed type. The existence of three phenotypes, M+N−, M−N+, and M+N+, is explained in that the last corresponds to the heterozygous, and the first two to the homozygous forms. Accordingly, the heterozygous form can be recognized directly. The implications of the hypothesis are shown in the next table.

Marriages	Progeny to be expected		
	M+N+	M+N−	M−N+
M+N+ x M+N+	50	25	25
M+N+ x M−N+	50	0	50
M+N+ x M+N−	50	50	0
M+N− x M−N+	100	0	0
M+N− x M+N−	0	100	0
M−N+ x M−N+	0	0	100

According to our observations, there were some exceptions to this rule, which prevented our final acceptance of the hypothesis. It is possible, however, that these exceptions are to be attributed to illegitimacy or to imperfections of the method of investigation, which is not as simple as that of the group determination; recently Schiff in his published observations on inheritance and population statistics was able to show complete agreement with the theory. Almost equally satisfactory are the recent unpublished results of Wiener.

If on further investigation the hypothesis should prove to be correct, the possibility of excluded paternity would be almost doubled, and a determination might be feasible in about a third of all cases. On the basis of the present data, it is, however, possible already to make statements having a considerable degree of probability. Further development may result from the inclusion of the subgroups of groups A and AB (Landsteiner and Levine, Thomsen), if additional observations confirm the supposed regularities.

The blood group reactions are more significant for practical medicine, in the case of transfusion. It would take us too far afield to enter more deeply into the history of transfusion, a history going back hundreds of years, to the time of the discovery of the blood circulation by Harvey. The possibilities of the operation were conceived even before that time, but, stimulated by Harvey's great discovery, it was first successfully carried out by Lower on dogs in the year 1666 in England, and during the following year the first transfusions of blood from animals to man were made by Denys in France, and Lower and King in England. Further efforts were directed toward the invention of special apparatus, and it was learned that it is not necessary to transfer the blood from vessel to vessel, but that also defibrinated blood may be used (Bischoff 1835). The first transfusion with human blood was probably made by Blundell during the first half of the 19th century.

How differently the operation was regarded may be illustrated by two points of view, cited by Snyder. In a "History of the Royal Society" (1607), Sprat stated: "Hence arose many new experiments, and chiefly that of transfusing blood—that will probably end in extraordinary success." Again, in a "History of the Royal Society" by Thompson (1812) it is stated: "The expected advantages resulting from this practice have long been known to be visionary." Not-

[9] Landsteiner and Levine.

withstanding all the efforts made, and the lively discussion of the problem, it was not possible to incorporate the procedure into medical practice, and the thought of its use had finally to be abandoned because the operation, while proving very useful in some cases, in others resulted in symptoms severe in character and even in death.

So far as the injection of animal blood was concerned, an explanation of the accidents was given by Landois, who as far back as 1875 discovered the phenomena of agglutination and hemolysis, which frequently took place when human blood was brought into contact with serum obtained from a foreign species. But it remained a mystery why the introduction of human blood into the circulation of man was at times dangerous, as it was considered a matter of course that the serum or plasma of the same species represents an innocuous medium, an assumption which was probably strengthened by the use of such sera in histological investigations.

The simple solution of the problem came in the discovery of individual blood differences and of the blood groups. Animal experiments, and particularly clinical experiences in cases where errors had been made in the determination of the blood groups, are confirmatory and leave no room for doubt that the transfusion of agglutinable human blood is, as a rule, accompanied by untoward consequences. The pathogenesis of shock following transfusion has, however, not yet been fully explained.

The first blood transfusion made on the basis of the agglutinin reaction was that of Ottenberg, but it was not until there arose the great need created by the world war that the method of transfusion from serologically selected donors was employed on a large scale and became definitely established.

It is not possible here to enter into details, such as the sources of error possible in the group determinations, their control through direct comparison of the recipient's with the donor's blood, and the precautionary rule of beginning the operation by the injection of small quantities of blood. It may, however, be mentioned that it is not absolutely necessary to employ blood of the same group, for we may also use other blood, for instance that of group O (see Ottenberg)—the cells of which are not influenced by the serum of any recipient. In the latter instance, however, it is necessary as a measure of safety to exclude donors with a high titre of agglutinins in their serum, as these may prove dangerous especially for severely anemic or weakened patients. The employment of the so-called "universal donors" of group O, or in general the use of inagglutinable blood of another group, may in an emergency and in the case of recipients belonging to the rare blood groups, be of great value.

Of the conditions indicating the employment of blood transfusion, the most important are acute and chronic anemia, that resulting from wounds, lung hemorrhages, in obstetrical practice, from tumors of the stomach and the intestines. The life-saving effect often produced in the case of hemorrhages is in the first instance of course attributable to blood replacement, and it is to be noted in this respect that the introduced erythrocytes may retain their function in the circulating blood over a period of weeks. Of significance also are the stanching of blood by raising the coagulability and probably the stimulation of blood regeneration in the bone marrow, as shown by changes produced in the histological blood picture. The great use made of blood transfusion in pernicious anemia has now become largely unnecessary through the discovery of liver therapy.

Another extensive field of application is in shock following severe injuries and operations. It is thought that in these cases the introduction of blood has a better effect than the injection of isotonic solutions, such as the common salt solution containing gums, employed by Bayliss during the war. According to these indications, apart from the blood replacement, transfusion can be employed with good results as a stimulant following major operations; in the case of weakened patients, American surgeons recommend its use even before severe operations.

Good results have also been obtained in haemophilia, thrombopenic purpura, and to a certain extent in agranulocytosis, CO poisoning, burns, while in a number of other diseases, for instance, the septicemias, in which transfusion was tried, the results have been uncertain.

Some figures which I presented before the International Microbiological Congress in Paris indicated the frequency of the use of transfusion therapy and the degree of comparative safety that has been achieved in this procedure, a result which in part at least is attributable to the considerable advances made in surgical technique. These statistics are not in entire agreement, as some authors, in contrast to others, still report occasional accidents. As these differences are probably ascribable to the technique employed in the procedure, I feel justified in basing judgment on the favorable reports provided they include a large number of cases.

The frequency of the operation is surprisingly great, and possibly it has at times been employed too extensively. According to statistics for which I am indebted to Dr. Corwin, of the New York Academy of Medicine, during the year 1929 there were about 10,000 blood transfusions given in New York City. In a recent publication of Tiber from Bellevue Hos-

pital in New York there are reported up to July, 1929, more than 1,467 transfusions made there in three and a half years. Among these transfusions, there were two deaths, one resulting from an error made in determining the blood group, and the other, also possibly avoidable, in an emaciated infant belonging to group A which received blood from a so-called "universal donor" of group O. Three deaths out of 1,036 transfusions reported by Pemberton, of the Mayo Clinic, were the result of errors in the determination of the blood groups. In Kiel, as I was informed by Dr. Beck, in the course of five years there were 2,300 transfusions given without a single death. In from 2 to 3 per cent. of the patients there were symptoms such as chills and a rise in temperature, which were, however, not of a severe character. A case of Beck's, one of pernicious anemia, is noteworthy: during a period of three and a half years, the patient received a total of 87 transfusions without any serious consequences.

Notwithstanding the favorable aspect of these results, there are reported, as said above, in addition to slight disturbances, exceptional severe and even fatal accidents which may not be attributable to errors in technique. It is not probable that in these cases the blood differences as indicated by the atypical isoagglutinins play an important rôle, in which event such accidents might easily be avoided. Whether, as has been assumed, injury can be caused by a marked pseudo-agglutination by the recipient's serum has not been definitely ascertained. Some of the disturbances appear to be due to allergy to food substances present in the injected blood, while others were ascribed to the action of antibodies formed as the result of former transfusions. The problem as to whether or not there are individual differences in protein which give rise to antibody formation has not been sufficiently investigated.

On the whole, the results obtained up to the present time with transfusion therapy are very satisfactory, and we may hope that an intensive study of the cases showing an unfavorable outcome will help to assess the significance of the supposed causes and reveal perhaps unknown ones, so that the slight degree of danger still attending the use of transfusions may be almost entirely averted.

Apart from the solution of this practical problem there is the possibility of developments resulting from the study of the biological aspects of individual serological differences in general, and particularly from the elaboration of procedures for finer differentiation of human blood and a continuation of the genetic analysis of serological blood differences in man and animals considering, that as a result of similar studies, we very probably possess to-day, apart from the sex chromosomes, knowledge of at least two pairs of human chromosomes which are marked by distinct characteristics.[10]

OBITUARY

JOHN HENRY COMSTOCK

Born in Janesville, Wisconsin, on February 24th, 1849. Died at his home in Ithaca, N. Y., March 20th, 1931. Between these dates, the career of one who rose from poverty and pioneer hardship to world service and honor.

HIS father was a frontier teacher, who died when the lad was three years old, and left him and his mother to struggle with want. At sixteen he became a sailor on the Great Lakes. Once in the course of his sailing when at anchor in the port of Buffalo, he visited a bookstore and came upon a copy of Harris's "Insects Injurious to Vegetation." Here was something that interested him beyond anything he had ever read. The illustrations fascinated him; but the price was beyond his means. He went sadly away. But he could not forego the possession of this precious book. He borrowed the money and returned and bought it; and this book had a large part in determining his future career.

At the age of twenty, though largely self-educated he was ready for college, and he entered Cornell University. That was in 1869, its opening year. He chose Cornell because there he could work his way; also, it was to be a place where in the words of its founder, one could "find instruction in any subject." So he came to study entomology.

But there was then no entomology at Cornell. There was, however, a sympathetic teacher of zoology, Dr. Burt G. Wilder, who promised the young man that he might work with insects to his heart's content. Under such friendly guidance his real work in entomology began.

So well did he work that he soon had a reputation for expert knowledge of insects; and so contagious was his enthusiasm that in the spring of 1872—his junior year—thirteen of his college mates petitioned the faculty to permit him to give them a course in entomology.

The request was granted. His teaching of entomology at Cornell began in a little room away up in the square tower of McGraw Hall, a building that had been built in part by the labor of his own hands. Later a department was created for him and in White

[10] While in press, an article on the subject was published by F. Bernstein, *Zeitschr. f. ind. Abst. u. Vererbungslehre*, 57: 113, 1931.