SPECIAL ARTICLES

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BLOOD GROUPS AND HUMAN GENETICS *

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No normal characteristic in any living organism has ever been investigated to such an extent or in such detail as the blood groups of the human species. The results of the determinations of just one of these characteristics, the ABO groups, in more than six million people from all over the world were published in the late fifties, and millions more have undoubtedly been examined. The reasons for this very widespread interest in a genetically determined character are mainly related to the fact that the blood groups have a completely unique position; they are almost completely independent of environmental factors such as disease, climate, nutrition, etc. and remain constant all through life, from its earliest stage. Even before any clear knowledge existed about the causes of variation between individuals with respect to the ABO groups, these erythrocyte peculiarities caught the interest of the clinicians who saw that by paying attention to these characteristics of the individual they were able to overcome most of the problems which for a long time prevented the safe use of blood transfusion as a therapeutic agent.

The first major contribution to the genetics of the blood groups came about 1920 when the Polish scientists L. and H. Hirszfeld described the phenomenon of population variations with regard to blood group frequencies. The studies of the Hirszfelds opened a new era in anthropology and population genetics. During the following years evidence from blood group studies added new or supplementary information to nearly all aspects of human genetics and confirmed the general applicability to man of most genetic principles originally established on the basis of experiments in plants or lower animals.

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It was not until about the middle of the twenties that the genetic basis of the ABO system was explained by Bernstein. Today it seems difficult to understand that nearly 25 years should have passed before an acceptable hypothesis fitting the observations could be worked out. It must, however, be remembered that the methods of genetic studies and analyses were far from fully developed at that time.

Many basic genetic principles were amply confirmed by the many family studies undertaken in the following decades, not only within the ABO system, but also within the numerous other systems disclosed later. It appeared that Mendel's laws were so uniformly correct that observations which did not fit with these laws could not be taken as a sign of the fallacy of these laws, but as an indication of wrong information about the sources of the genes of a given individual, i.e. about his or her biological parents.

In quite a few countries these facts have been fully accepted; among the practical applications of the blood groups their use in clinical medicine as a prerequisite for blood transfusion, is undoubtedly the most important, but next comes their application in problems of parentage, especially paternity which is almost exclusively based on the use of blood groups.

Problems concerning the spatial arrangement of the genes on the chromosomes occupied the minds of general geneticists from a very early date, but it was impossible to attack this problem in human genetics to any greater degree until the knowledge of blood group systems had been extended. So far, it is only through the use of blood groups that it has been possible to demonstrate the phenomenon of autosomal linkage and of crossing-over in man.

The very great contribution which blood groups have made towards clarifying the relations between populations, population movements and mixtures, makes a large field of its own. It should only be mentioned that one should never rely upon the results of blood group determinations in just one or two systems as it is known that the blood group distribution of a popuplation may be subject to chance influences or even to influences of a more specific nature. If many blood group systems show the same trend, this can be taken as an indication of genetic relationships.

In this highly specialized field, the future still looks very promising, as most of the blood and serum group systems discovered

recently show great variations between population groups. As an example we may take the Diego system in which Caucasians as a rule are negative, but the American Indians, the Japanese and the Chinese show varying, but relatively high frequencies of Diego-positive individuals. Careful and extensive blood group studies allow good estimates to be made of the degree of intermixture such as the amount of Causacian genes which can be found in the gene pool of the American Negro. Much more information is still needed, for instance from Eastern Siberia, before it is possible to elucidate the genetic relationship between American Indians and the Asian populations.

It ought to be mentioned that blood groups are not the only characteristics of value in this type of research, although for a long time they were considered more important than other traits, due to their supposedly selective neutrality. Serious doubts were often raised about this neutrality because it was difficult to explain the world wide variations of the blood groups. It was suggested that some phenotypes probably conferred advantages on the bearer while other phenotypes might present disadvantages.

The first support of these views came in the beginning of the fifties, not as a result of a systematic search for evidence of this type, but as a result of a study which aimed at explaining variations with regard to mortality from cancer of the stomach which had been observed between various regions in Great Britain. It appeared that cancer of the stomach was associated, *not* linked, with blood group A; later it was shown that duodenal ulcer was associated with blood group O and with non-secretion of ABH-antigens. It has been estimated that people with this constellation of phenotypes, O-nonsecretor, run a risk of developing ulcer 240 per cent more than the risk found in people of other blood groups. In operations for ulcer, where an anastomosis is considered, it is worth remembering that individuals with the blood groups mentioned are very much more prone to develop stomal ulcer. A few other diseases, most of them connected with the gastro-intestinal tract, have likewise shown associations with one or another of the ABO blood groups, but no indications of associations with other blood groups have appeared so far.

The explanation of these observations is not known; the chemical composition of the substances carrying the characteristics of the ABH-antigens is almost the same in people of different blood groups. It was for some time suspected that stratification of the population could be an explanation, with some subpopulation

having, for instance, a high frequency of O and genes determining the development of ulcer, but this has been ruled out. Even if these findings demonstrated that blood group genes are not neutral, the disease associations observed could not be of decisive importance in the explanation of blood group variations. To be effective, the associations had to be with diseases appearing much earlier in life and thus interfering with reproduction, that is to say, some blood groups should make the bearer more sensitive to one or another fatal disease which would prevent him from having the average number of children and, thus, from giving his share to the composition of the gene pool of the next generation. In this way some genes would, relatively speaking, be underrepresented and some overrepresented in the following generations.

Some years ago it was suggested that the great plague epidemics of previous centuries could be made at least partly responsible for the variations because it was noted that blood group O was lowest in the centers of those epidemics, but higher in small islands, mountains and other isolated areas where the plague had not been introduced. Furthermore, it looked as if blood group A was more prominent in those parts of the world where smallpox had occurred only rarely.

Some investigators thought that experimental evidence along these lines supported this theory. An antigen was found in vaccinia virus extracts which closely resembled blood group A antigens. If this were the case, people of blood group B or O with anti-A in their serum would be expected to show more resistance against small-pox virus infection. Later it was doubted if this A-like antigen derives from the virus; it might derive from the cells on which the virus was grown. Some supporting evidence has, however, come from a comparison of the severity of smallpox in patients of various blood groups. Some investigators have found that the course of the disease was significantly more severe in patients of group A. This may or may not be an essential part of the explanation of the present day variations in different parts of the world. In any case it makes it probable that differential mortality, related to the blood groups and appearing at an early age, may have caused changes in blood group gene frequencies in a rather short time.

It may be too late to demonstrate the most important associations with diseases because of the great reduction in infant and child mortality in the last 100 years which has changed the relative im-

portance of the possible causes of early death. A genetically important association between a blood group and some common disease of childhood may have existed some hundreds of years ago which may be relatively unimportant now due to the more or less complete eradication of the disease in question. It might be mentioned in this connection that analyses of this type are obscured by our inability to make any direct distinction between heterozygotes AO and BO and homozygotes AA and BB, respectively. More clearcut results might be expected when this problem is solved.

It has been shown that blood groups, or at least some of them, are subject to natural selection in a more direct way. This has been made clear when the hemolytic disease of the newborn, due to Rhesus incompatibility, was explained in the beginning of the forties. In this connection it was also demonstrated how genes from completely different loci may interact, probably a phenomenon of wider importance. The fact that ABO incompatibility could protect against Rh hemolytic disease was an illustration of gene interaction of a more complicated nature.

At the end of the fifties and at the beginning of the sixties very elaborate statistical techniques applied to large bodies of family data have shown that blood group incompatibility between mother and fetus may be an important cause of prenatal loss, and probably of very early loss. The errors of anamnestic reports on fetal loss are eliminated by blood group segregation analyses in families where significant reduction of one of the expected groups of offspring reflects mortality at early stages of development much more precisely than the most accurate registry of fetal deaths. It has been shown that ABO maternal-fetal incompatibility causes the elimination of about 10 per cent of all incompatible zygotes. Few loci are as important as the ABO locus in this connection. The published materials on fetal loss do not permit an evaluation of the time at which this loss occurs. Although clinical hemolytic disease of the newborn is almost exclusively restricted to children of group O mothers, it can be shown that even A and B mothers give birth to fewer incompatible children than expected. These observations demonstrate the great and serious influence of seemingly neutral characteristics and they also help in explaining the polymorphism of human blood groups. The ABO polymorphism may be maintained because heterozyogote advantage in compatible matings more than compensates for selection against heterozygotes in incompatible matings. The possibility of antigenic selection of the sperm in the female

reproductive tract should also be studied in detail. The evidence is still very limited, but it is known that uterine secretions may contain hemagglutinins and that sperms carry ABO antigens.

It is quite clear that all these very essential problems concerned with the ways and means of natural selection in man could never have been elucidated to such an extent without the very extensive knowledge which has by now been accumulated about the blood groups of man. Thus, the work within many of the fields of human genetics has got and still gets its main observational support from the study of blood groups. The recent additions to this collection of normal characteristics, the serum groups, may be expected to add even more to our knowledge of human genetics in general.