Forum

Associations between hereditary blood factors and diseases

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The first suggestion that the ABO blood groups, discovered by Landsteiner in 1900, might be involved in the etiology of a disease was made as early as 1905 by Dienst. He clearly demonstrated isoimmunization by pregnancy and suggested that susceptibility to pregnancy toxaemia was partly dependent upon the mother's blood group.

The next two vital steps in the history of the subject were both taken by L. Hirszfeld, who with von Dungern showed that the blood groups were inherited as Mendelian characters (von Dungern & Hirszfeld, 1910). It thus became clear that human populations were genetically polymorphic, and in 1918–19 Professor Hirzsfeld and his wife first showed that the frequencies of the blood groups (and hence of the genes determining them) differed widely between different ethnic groups.

The discovery of the MN and P blood group systems by Landsteiner & Levine (1927; 1928a, 1928b) and of the Rhesus groups by Landsteiner & Wiener (1940) greatly enlarged the field of human blood polymorphisms, and the finding by Levine et al. (1941) that Rhesus incompatiblity between mother and fetus was the main cause of erythroblastosis fetalis (haemolytic disease of the newborn) confirmed and dramatically underlined Dienst's discovery of functional significance in the blood groups.

Since 1941 many new systems of blood groups in the narrow sense (i.e., haemagglutinogens) have been discovered, and genetic diversity has been shown to characterize many other constituents of the blood—the plasma proteins, the haemoglobins, the red-cell enzymes, and antigens present in the leucocytes and platelets—so that it is now possible to list about 60 systems of genetic polymorphism affecting the blood, a polymorphism being regarded as a system characterized by two or more allelomorphic genes, the rarer or rarest of which has, in at least one population, a frequency too high to be maintained solely by chance mutation. Moreover, for nearly every system for which a variety of ethnic groups have been surveyed, gene frequencies have been found to vary widely.

Ever since it has been realized that such polymorphisms are common and that gene frequencies are variable there have been two main schools of thought among those attempting to account for the observed phenomena. Both schools have, of course, looked to mutation to supply the raw material for the polymorphisms. On the one hand there have been those who, following Sewall Wright, have attributed to chance fluctuations the differences found between populations. On the other hand, following the general guidance of R. A. Fisher and the more specific statement of E. B. Ford (1942), attempts have been made to account for such differences in terms of natural selection, different genes being favoured initially in different environments. This would ultimately lead to different states of balanced polymorphism, with stable gene frequencies maintained in equilibrium dependent on the environment.

There is no doubt that random processes have a large influence on the genetic constitution of small populations, of populations (such as the Dutch in South Africa and some religious minorities in America) that stem from a small number of founders, or that have at some time, as a result of catastrophe, diminished to very small numbers (but in this case the catastrophe itself may have been selective). Furthermore, it is now becoming clear that many thousands of different proteins exist in the human (or any other metazoan) body, each produced by a different gene and each gene subject to mutation. Moreover, it is probable that the polypeptide chains of most of these proteins have gradually lengthened in the course of evolution, and that certain parts of the chains, though retained, have lost their function. This is just as likely to have happened to blood proteins as to any others.

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In such parts of the molecules mutations will inevitably have occurred and it is likely that, in the course of millions of generations, polymorphisms have developed, by chance, frequency fluctuations almost totally unrelated to selection. But those parts of the molecules that have remained functional must also have been subject to mutation, and it is equally likely that the environment has had a selective effect on them. Indeed, the whole process of evolution by natural selection is now seen to be the result of such effects. However, nearly all the body characters such as shape, size, and colour, which are accepted as resulting from natural selection, are each the product of numerous genes, and little has been done so far in the higher animals or in man to isolate the effects of the single genes involved. Thoday (1961) has, however, made a beginning of such an analysis for *Drosophila*.

However, if we are ever to understand the evolution of our own species, it is important not only to attempt the very difficult genetic analysis of the polygenic characters, but also to search for selective effects and to attempt to measure them in the case of genetically simple characters so many of which are now becoming available for the purpose.

We have seen that there probably exist blood protein polymorphisms that have virtually no effect on the function of the proteins concerned and so are almost solely the result of long-term random processes. At the other end of the spectrum there are blood diseases, such as haemophilia, that have such a high mortality that, whatever the environment, they are maintained almost entirely by recurrent mutation. Even in this case, however, modern medicine would, in the absence of eugenic measures, create an " environment " in which a true anti-haemophilic globulin polymorphism could build up.

I am concerned in this article, however, with examining the intermediate part of the spectrum —that of the polymorphisms where none of the variants has any obvious effect on health but where epidemiological methods show that, in certain extreme environments, such as exposure to certain infections, one allele is more favoured than another. This part of the spectrum certainly exists, but we do not yet know how broad it is or how important for human welfare. In my opinion, it is likely to prove very important, and it merits a much greater research effort than has hitherto been devoted to it.

A classical example of interaction between a blood polymorphism and the environment is that of the haemoglobins. Sickle-cell anaemia, which affects homozygotes for the gene for haemoglobin S, is comparable in lethality to haemophilia, yet in parts of Africa the Hb S allele of the gene for normal adult haemoglobin, Hb A, reaches frequencies as high as 20%, so that a true polymorphism is present. The maintenance of this was for years a puzzle to geneticists, until Allison (1954) proved what had been suspected for some time: that the AS heterozygotes are substantially more resistant to malignant tertian malaria (due to *Plasmodium falciparum*) than normal persons are. Thus malaria kills many of the AA homozygotes, anaemia kills most of the SS homozygotes, and both genes are passed on to the next generation by the favoured AS heterozygotes. In this way, a balanced polymorphism is established, the frequency of the Hb S gene being closely related to the degree of endemicity of falciparum malaria.

Two other blood polymorphisms—that for β-thalassaemia and that for glucose-6-phosphate dehydrogenase (G6PD)—appear to bear a similar relationship to malaria, but the evidence is not as complete. The maintenance of the thalassaemia polymorphism in certain populations through differential resistance to infection was the subject of a classic prediction by Haldane (1949), but the evidence that has since been obtained for the relationship to malaria is almost entirely epidemiological. Evidence for the protection afforded against malaria by certain G6PD variants (chiefly those characterized by deficient enzyme activity) is mainly epidemiological, but it is supplemented by several studies showing direct protective effects (Allison & Clyde, 1961; Harris & Gilles, 1961; Bienzle et al., 1972). It must be admitted that the analogy with the blood groups is not a complete one, since sickle-cell haemoglobin, β-thalassaemia, and the " deficient " forms of glucose-6-phosphate dehydrogenase, unlike the blood groups, have specific and observable harmful effects. However, Bienzle et al. have shown that the A+ form of the last-mentioned enzyme, which seems to be without any harmful effect and is common in most African populations, also has a protective effect against *P. falciparum* infection.

We possess no such dramatic evidence for the mechanism of maintenance of the blood group polymorphisms. Their most striking clinical effect (apart from the modern and totally artificial blood transfusion situation) is in the production of haemolytic disease of the newborn. In a proportion of those pregnancies where the fetus possesses an antigen lacking in the mother, the latter becomes immunized to it and her antibody then damages

the red cells of subsequent fetuses with the same antigen. The Rhesus and ABO systems—and to a lesser extent the Kell, Duffy, and other blood group systems—can become involved in this process. However, apart from certain obstetric techniques, the environment appears to have no influence on the process of immunization and no convincing theory has been put forward that would make it responsible for a balanced polymorphism, though it might shift a balance set up by other mechanisms.

Another effect of blood groups on disease incidence follows logically at this point, though it is in fact a very recent discovery. This concerns the influence of the ABO blood groups of a woman and her husband on the incidence and progress of chorioncarcinoma (Bagshawe et al., 1971). This type of carcinoma, whether it follows a normal pregnancy or a hydatidiform mole, is a neoplasm of fetal tissue and would be expected to possess the immunological characters of a fetus, including the presence of ABO antigens inherited from the husband. The data consist mainly of the ABO groups of affected women and their husbands. The relative incidences of the disease in the presence of various combinations of blood groups are partly explained in terms of the protection that a woman would be expected to enjoy against a carcinoma arising from an ABO-incompatible pregnancy—i.e., one against which she possesses an antibody, especially anti-A. However, in the case of A women, those married to O men are shown to be at greater risk than those married to A men, though in neither case should the conceptus contain an ABO antigen not present in the mother. It is tentatively suggested that in some way an O trophoblast reacts to the foreign A antigen present in the mother. Moreover, the prognosis is particularly serious in the case of an AB woman—to an even greater extent than would be expected solely from the fact that she possesses neither anti-A nor anti-B. But this disease is a very rare one and can have no appreciable effect in modifying the frequencies of the ABO groups in a population.

This relationship to the ABO groups was, however, not known 20 years ago, and the development of studies of the blood group polymorphisms at this time followed from the failure of the incidence of haemolytic disease of the newborn to explain the existence of these polymorphisms and the varying gene frequencies found in different populations. The most important relevant line of investigation was then, and has continued to be, the determination of the blood groups (mainly at first ABO and Rh) of large series of persons suffering from particular diseases. It can now be seen that much of the early work was based on numbers too small to give statistically significant results, and the first fully convincing data were those published in 1953 by Aird et al., who showed that among persons suffering from carcinoma of the stomach there was a highly significant excess of group A as compared with the general population. The most likely explanation for this appeared to be that persons of group A, in the same environment, were more likely to acquire the disease than persons of other blood groups. An alternative hypothesis was that the British population was stratified, one stratum having a high incidence of both carcinoma of the stomach and group A, and another stratum having a low incidence of both. However, the same association of blood group and disease has now been found in numerous surveys in many countries and in populations of widely different racial origins, so that not only is the stratification hypothesis disproved but the statistical evidence for the association is overwhelming. The mechanism by which it arises is, however, still quite obscure, though it may be related to the immunological properties of the carcinoma cells.

Another highly instructive series of investigations was that initiated by Aird et al. (1954), who showed the existence of a significant excess of group O among patients suffering from peptic ulcers (gastric and duodenal). Clarke et al. (1955) confirmed this but showed that it was almost, if not entirely, confined to duodenal ulcer. Clarke et al. (1956) then showed a marked association also with the hereditary character of nonsecretion of the antigens of the ABO system in the saliva. These associations have been abundantly confirmed in subsequent years on large numbers of cases and in numerous ethnic groups, but always or nearly always on hospital patients. The association with group O was for some years generally accepted as being due to a true increased susceptibility of persons of group O to duodenal ulcer, but one puzzling feature was the low correlation between blood groups and the occurrence or non-occurrence of duodenal ulcer within sibships (though there is a marked correlation with the absence of secretion). It has since been shown by Langman & Doll (1965) and confirmed by other workers that, among known cases of duodenal ulcer, those of group O are especially likely to bleed. Thus the bleeding tendency, which will tend to bring patients to hospital, may account for

much or even all of the excess of group O previously found among patients hospitalized for duodenal ulcer. However, the observed association between duodenal ulcer and the absence of secretion of blood group substances in the saliva cannot be explained in this way, for the same authors found that the absence of secretion, among the patients whom they investigated, was associated not with bleeding but with an increased tendency to need surgical intervention. There is therefore probably, as the sibship studies suggest, a true association between ulceration and the absence of secretion.

Meanwhile numbers of workers had published papers suggesting an association between blood group A and various thromboembolic diseases. This was particularly striking, in spite of small numbers, in the series of young women taking oral contraceptives investigated by Jick et al. (1969). It gradually became clear that haemorrhage tended to be associated with group O, and thrombosis with group A, and that both associations might be related (as suggested by Jick et al.) to the higher average level of antihaemophilic globulin in the plasma of A than in that of O persons. Numerous workers contributed to this synthesis, and the work has been summed up, with a full bibliography, by Mourant et al. (1971).

A number of other diseases appear to be associated with particular blood groups, especially carcinoma of the uterine cervix and pernicious anaemia with group A and rheumatic heart disease with a lack of group O and with non-secretion of ABH. Claims have been made for the existence of numerous other associations—some probably genuine but many based on inadequate statistical evidence. Moreover, carcinoma of the stomach, bleeding duodenal ulcer, and indeed most of the diseases for which associations have been claimed, are not important killers before or during the reproductive period and hence are unlikely to have played a major part, through natural selection, in altering the blood group frequencies of whole populations. The important killing diseases of the young, apart from war injuries and starvation, have been the great epidemic infections. If any of these were shown on adequate statistical evidence to be more lethal to persons of one blood group than another, natural selection affecting the blood group frequencies of populations could be regarded as proved.

Since the occurrence and severity of infections are largely the results of the immunological response of the body to invading organisms, it would not be unexpected if the blood group of an individual were found to be one of the factors determining such a response. A very large amount of work has been done on the *in vitro* immunological relations between the antigens of microorganisms and those determining the ABO blood groups, but only in a very few cases have the essential epidemiological field studies been carried out. Probably the most extensive studies of both kinds are those that have been carried out on smallpox and the immunologically closely related vaccinia. Vogel et al. (1960) investigated the immunological relationships, to the ABO blood groups, of the organisms responsible for plague, smallpox, and cholera. They asserted that the plague organism, *Pasteurella pestis*, possesses an antigen similar to the human H, which is most abundant in persons of blood group O, whereas vaccinia virus possesses an A-like antigen. They further showed that the modern distribution of the ABO groups is consistent with the possibility that persons of group O lacked resistance to plague and those of group A, to smallpox. Springer & Wiener (1962) severely criticized their work, and especially the *in vitro* immunological results which, they claimed, were artifacts resulting from the methods of culture of the organisms. Pettenkofer et al. (1962) published a reply. These papers and many subsequent ones have dealt with *in vitro* relationships, without reaching any semblance of a final conclusion.

Although the attempt to define an immunological background to relations between blood groups and diseases is most important, it has relatively little interest in the present context unless epidemiological investigations are carried out and show a relationship between the blood groups and susceptibility to the disease in question. Vogel and his colleagues have carried out numerous such investigations in the case of smallpox and vaccinia; their results show a positive relationship between group A and susceptibility to smallpox and to some complications of vaccinia (see Vogel & Chakravartti, 1966), whereas other workers (Downie et al., 1965; Bourke & Clarke, 1965; Bourke et al., 1965) found no such relationship. There is no reason to doubt the results of any of the investigators, but it is desirable that others should carry out similar investigations under precisely defined conditions; it is important also that the extensive published results should be fully analysed statistically to see how far they are incompatible with one another and whether the stated methods of investigation differ systematically between the

various sets of results. One possible kind of outcome of such an analysis may be illustrated by the recent study of Mourant et al. (1971) on the relationship that has been claimed to exist between group A and susceptibility to coronary artery disease. They found a marked relationship, but the published data showed a high degree of heterogeneity. This was explained when it was found that series of cases of coronary thrombosis and of its sequel, cardiac infarction, showed a marked and homogeneous association with group A, whereas series of cases of coronary insufficiency without reported thrombosis showed a low and statistically nonsignificant association.

A few other main infectious diseases show significant associations with blood groups. McDonald & Zuckerman (1962) have demonstrated an association between blood group O and influenza of type A_2; Clarke et al. (1960) have found a marked association of rheumatic carditis (which is a late sequel of haemolytic streptococcal infection) with blood groups other than O, and with the absence of secretion of the ABH blood group substances. In view of the apparently contradictory results of the smallpox investigations it is important that both the apparent associations just mentioned should be investigated by other workers, and especially that they should be sought in non-European populations.

The primary need in every case is for soundly planned epidemiological surveys, but where positive results are obtained attempts must be made to relate them to pathogenic processes.

The associations of blood groups with haemolytic disease of the newborn and with susceptiblity to chorionepithelioma are readily explained in terms of existing immunological knowledge, even if the implications in terms of gene-frequency equilibrium are not fully understood. Associations of infectious disease with blood groups are likely to be explicable in immunological terms and, with growing knowledge of the immunology of neoplasms, associations in this field should present no long-term problem. However, the normal functions of the blood groups are still unknown—it may be that work on associations between them and diseases will be the key to that knowledge, but at present the approach to studies of associations must be largely empirical.

It is otherwise with the protein components of the blood, the plasma proteins, the haemoglobins, and the red-cell enzymes. Most of these have precisely known functions and large numbers of them show genetically determined polymorphism. In a considerable proportion of the latter, the products of the different alleles (of, for instance, a given enzyme) differ quantitatively in their chemical activity. There thus exists a well-understood physicochemical background to guide a search for associations between genetic variants of a given protein, on the one hand, and response to a particular infection or other hazardous feature in the environment, on the other.

The best example so far demonstrated of such an association in man is one involving the ABO blood groups and the haptoglobins. As has been shown by Ritter & Hinkelman (1966), by Kirk et al. (1970), and by Kirk (1971), in family studies on a wide variety of populations, the Hp^1 frequency in offspring is higher in families where the father possesses an A or a B antigen not present in the mother than in those families where he does not. This is almost certainly related to the fact that the Hp^1 protein is more efficient than the Hp^2 in removing free haemoglobin from the circulating blood and conserving it for the production of new red cells. Thus it appears that, in cases (probably far more numerous than are recognized clinically) where children are suffering from haemolytic disease of the newborn as a result of maternal immunization to fetal A or B inherited from the father, a child who is of type Hp 1-1 has the best, and one who is Hp 2-2 the worst, chance of survival, Hp 2-1 being intermediate in effect. The precise means by which both ABO and Hp frequencies are presumably conserved from generation to generation, so that A, B, and Hp^2 genes do not die out in the long run, are not yet fully understood.

The other main plasma protein involved in iron conservation is transferrin, which takes up inorganic iron from the plasma and transfers it to the bone marrow. Variants of the common type are rare in nearly all human populations, but in cattle Ashton (1965) has demonstrated a balanced polymorphism of transferrin types, involving mainly differential fertility. It would be of interest to study human fertility in relation to transferrins in such populations as the Melanesians, Australian aborigines, and South American Indians, all of whom have high incidences of transferrin variants.

Bottini et al. (1972) have found, in a single series of observations, that homozygotes for the placental alkaline phosphatase gene Pl^f_1 are protected against haemolytic disease of the newborn resulting from B immunization but not from A immunization of the mother.

In man the genetic variants of the plasma and red-cell proteins are comparatively new discoveries, and few studies have yet been made of their relation

to diseases. However, the discoveries just mentioned suggest that they will prove a fruitful field for the study of balanced polymorphism related to environmental conditions.

One other biochemical polymorphism, affecting not the blood, but the tongue and the thyroid, is the taster–non-taster polymorphism for response to a group of substituted thioureas, all of which are also antithyroid substances. Some of these have been used as antithyroid drugs; others occur naturally in food plants.

A knowledge of these facts led Harris et al. (1949), and subsequently Kitchin et al. (1959), to investigate the distribution of taste sensitivity in human cases of thyroid disease. Both groups of authors agree that there is a lowered frequency of tasters in nodular nontoxic goitre, and Kitchin et al. also found a significantly raised frequency of tasters in patients with diffuse toxic goitres. Several subsequent investigations in different countries have confirmed these results. However, in the Japanese, who normally have a rather low frequency of non-tasters, and in South American Indians, who have an extremely low frequency, no significant association between goitre and tasting could be found. Most of the early series of nontoxic goitres were sporadic rather than endemic, but it is important to notice that in the Netherlands and in Israel persons with endemic goitre showed a lowered frequency of tasters.

This association is now fairly widely known, but the same is not true of the work of Widström & Henschen (1963), who have shown that in persons without overt thryoid disease there is a statistical correlation between the level of protein-bound iodine in the serum and the ability to taste PTC, persons with a high iodine level being more frequently tasters than those with a low level. This work appears convincing and is consistent with the observations on goitrous persons, while suggesting that the goitrous cases represent the clinically abnormal extremes of the normal thyroid function range. Unfortunately no very extensive further study has been carried out on these lines, but the results have been confirmed on a relatively small scale by Becker et al. (1966)—one of many groups of workers to have investigated a possible association between the taster polymorphism and different types of glaucoma. A further indication that the taster phenomenon is of importance in relation to the endocrine balance of healthy persons is the finding by Johnston et al. (1966) of a tendency to earlier pubertal development in tasters than in non-tasters.

Several of the associations claimed between polymorphisms and disease are completely convincing; a great many more are likely to be genuine and, if so, are of great importance in the study of man's relation to his environment. Note must however be taken of a number of serious pitfalls that lie in the path of investigators in this field, many of which are listed in the adversely critical papers of Manuila (1958) and Wiener (1970). Those criticisms that refer to statistical conventions and methods, such as fiducial limits, and the methods of combining data from different populations, have been very fully and soundly dealt with by Roberts (1959), and his discussion of this aspect of the subject will not be repeated here. There are, however, serious possibilities of error in the nature of the data used in the studies, and these must always be kept in mind and avoided. They will be considered here, though most of them have already been discussed by Roberts.

In reputable hospitals and research centres the accuracy of blood grouping is no longer a problem, but in field studies under difficult conditions only experienced workers can be confident of obtaining correct results. The results of some observations, both on patients and controls, must be subject to suspicion of error on this account. Diagnosis of the disease must be made by a competent clinician who is unaware of the blood group results. However, a small proportion of wrong diagnoses will not substantially affect the validity of a series of results, for it will simply dilute the sample of patients with a small proportion of persons having almost certainly the same blood group frequencies as the control series, and so will slightly—but only slightly—reduce the apparent significance of a positive result.

Much more important is the requirement that patients and controls should be drawn from the same interbreeding population. In a socially and ethnically homogeneous population, served by a well-organized volunteer blood transfusion service, the records of this service will, in my opinion, give the best available control data, but only if records can be obtained of the total recruitment to the service, over a given period, of persons who when they joined the service did not know their own blood groups. The active donor panel taken by itself has usually been subject to selective resignation and will almost invariably give erroneous results. The consistency of the blood group frequencies in the control panel with the Hardy–Weinberg law is an important check on their validity. However, it is desirable, whenever

possible, to include a second control series consisting of the blood groups of patients admitted to the same hospital for reasons unlikely to be related to blood groups, such as accident surgery.

The designation of a valid control series is perhaps the most difficult part of any survey of disease associations; it depends greatly on the balanced judgement of the investigator, who should describe very fully how the controls were chosen, In general, however, where there is a real association of a disease with a particular blood group, the frequencies in the series of patients will differ from those in the controls by a much wider margin than any differences that might arise from errors in the selection of controls.

Another serious source of possible error lies in the nonpublication of negative results. In the case of common diseases large series of cases will be published and each series will be able to stand by itself. However, in the case of rare diseases there is a danger that, once an initial series has been published, showing an apparent (but perhaps statistically nonsignificant) association, there will be a temptation for other workers to publish further small series that support the first results but to fail to publish those that do not. There is no way of preventing this completely, but there are some partial remedies. In any one country an attempt should be made, through specialists in the particular disease, to coordinate all surveys that are planned. It would be helpful also if at least a brief note could be published on every survey result submitted, whether it shows an association or not.

The possiblity of a genetic stratification of the population studied must always be borne in mind. Where there is an obvious stratification shown, for instance, by colour, it is possible to separate the disease series and compare each with its own control series. The results can then be combined with full statistical validity by, for instance, the method of Woolf (1955). The presence of more subtle forms of stratification, for instance by religion in a physically homogeneous population, presents a more difficult problem. However, in the case of common diseases, such as carcinoma of the stomach and bleeding duodenal ulcer, the problem has finally been solved by finding the same associations in populations of widely differing ethnic origins.

The demonstration of associations between various genetic markers and susceptiblity to particular diseases is an important contribution to human genetics and it is throwing new light on the mechanisms of man's evolution. However, whereas the study of blood groups and of tissue types forms an essential part of the methods of blood transfusion and tissue grafting, respectively, and blood group tests are essential in the treatment of haemolytic disease of the newborn, it is only very gradually that other associations are being accepted as relevant to clinical medicine.

Certain associations have been shown to be of substantial prognostic significance and will probably influence treatment in time. For instance, an AB woman who contracts chorionepithelioma is at particular risk and should therefore be treated very promptly. An A woman taking an oral contraceptive is in substantially greater danger of thrombotic episodes than an O woman, and in borderline cases this could affect the decision which contraceptive to use.

Moreover, as clinicians gradually come to accept statistics as an essential part of medicine, and especially as diagnosis becomes assisted by the computer, a knowledge of a patient's blood group and other marker genes will be among the many factors to be taken into consideration in reaching a diagnosis. However, it is perhaps in epidemiology, in the broadest sense, and in geographical pathology, with its stress on interaction between the genome and the environment, that the study of associations between inherited blood factors and diseases will find its most important application. These fields are, moreover, of particular interest to WHO. For instance, goitre surveys in developing countries have hitherto been regarded as relating almost solely to the amount of iodine and perhaps other substances in the diet. However, Cartwright & Sunderland (1967) have pointed out that in England the geological and chemical environments in Derbyshire and North Lancashire are almost identical, and have suggested that the higher incidence of goitre in Derbyshire is probably related to the lower frequency of PTC tasters in this region. Such a finding may prove relevant on a world scale. The relevance of abnormal haemoglobin surveys to malaria incidence is now widely accepted, and if it can be shown conclusively that susceptiblity to other major epidemic diseases is related to recognizable genes, the world distribution of these genes will need to be studied as part of the strategy of the fight against epidemics.

ACKNOWLEDGEMENTS

The preparation of this paper was supported by a grant from the World Health Organization.

RÉSUMÉ

ASSOCIATIONS ENTRE LES CARACTÈRES SANGUINS HÉRÉDITAIRES ET LES MALADIES

Les groupes sanguins ABO ont été découverts par Landsteiner en 1900 et le type mendélien de leur transmission héréditaire a été démontré par von Dungern & Hirszfeld en 1910. En 1918-19, Hirszfeld & Hirszfeld ont, les premiers, montré que les fréquences des groupes sanguins variaient fortement entre groupes ethniques différents. De telles différences ont été trouvées pour chaque système de groupes sanguins, groupes sériques et enzymes érythrocytaires découverts par la suite. L'origine et le maintien de ces différences étaient attribués à la dérive génétique d'une part et à la sélection naturelle d'autre part. Si l'on admettait le rôle de cette dernière, on était logiquement amené à soupçonner l'existence de corrélations entre les maladies et les caractères spécifiques du sang.

La mieux établie de ces corrélations est l'association entre les hémoglobines Hb A et Hb S et le paludisme. La plupart des homozygotes SS meurent dans le jeune âge d'anémie drépanocytaire. Beaucoup d'homozygotes AA exposés au paludisme à *Plasmodium falciparum* succombent à l'infection. Les hétérozygotes AS ne souffrent pas d'anémie falciforme et ils résistent mieux au paludisme. Ainsi favorisés, ils transmettent de génération en génération le gène Hb S dont la fréquence se maintient et est fonction du degré d'endémicité du paludisme.

Il importait d'étudier la possibilité de corrélations entre d'autres maladies et d'autres caractères sanguins. Le premier exemple convaincant en a été fourni par Aird et al. en 1953, qui ont montré que parmi les patients atteints de cancer de l'estomac on comptait une proportion élevée de sujets de groupe A. Cette relation ayant été retrouvée dans les ethnies les plus diverses, il semble certain que les individus de groupe A sont plus exposés au cancer de l'estomac que les individus d'autres groupes. Parmi les malades souffrant d'ulcère du duodénum, il y a davantage de sujets présentant le caractère héréditaire de non-sécrétion des antigènes ABH dans la salive que parmi les personnes bien portantes. Chez ceux d'entre eux qui ont une tendance aux hémorragies, on note une fréquence élevée du groupe O.

D'autres corrélations entre des maladies et les groupes sanguins sont déjà assez bien établies: le cancer du col utérin et l'anémie pernicieuse avec le groupe A; les thromboses avec le groupe A; la grippe de type A2 avec le groupe O; la cardiopathie rhumatismale avec la non-sécrétion d'ABH et les groupes autres que O. Des relations plus compliquées existent pour les polymorphismes des protéines du sang.

La faculté héréditaire de goûter le phénylthiocarbamide (PTC) s'observe avec une fréquence élevée chez les malades atteints de thyréotoxicose (maladie de Basedow) et avec une fréquence diminuée chez les porteurs de goitre nodulaire non toxique. Chez les sujets bien portants, il existe une corrélation positive entre le taux sérique de l'hormone thyroïdienne et l'aptitude à goûter le PTC, ce qui peut avoir des conséquences physiologiques importantes.

Ce sont évidemment les épidémies qui affectent la mortalité des populations dans la plus grande mesure, et cela indépendamment de l'âge des malades. Si l'on pouvait montrer que la possession de tel ou tel caractère génétique expose davantage à la contagion, l'influence sélective des épidémies serait établie. Toutefois, les recherches dans cette direction sont encore l'objet de controverses.

Il va sans dire que les études portant sur les relations entre les polymorphismes et les maladies sont très exposées aux risques d'erreurs, erreurs de technique d'abord et erreurs d'interprétation statistique ensuite. Ces écueils peuvent cependant être évités et les résultats à obtenir dans ce domaine revêtent une grande importance pour l'épidémiologie et, éventuellement, pour le diagnostic et le traitement des maladies.

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