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Blood Groups, Disease, and Selection

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INTRODUCTION

After the discovery of the ABO blood groups by Landsteiner in 1900, many unsuccessful attempts were made to find associations between the blood group antigens and disease. The view was held, therefore, that the phenotypes controlled by the genes determining blood group specificity were of neutral selective value. The explanation offered for differences in the distribution of the genes in different peoples of the world was the drift of gene frequencies in different populations or of sampling variation in small populations. When the total human population of the earth was small and man lived in small groups, especially in geographically isolated areas, the frequency of one gene may have risen by chance to high proportions. Drift probably was responsible, for example, for the high frequency of blood group A (80%) in Blackfoot and Blood Indians compared with 2% in the Ute Indians of North America. In Europe, populations such as the Basques and Lapps, which have inbred for thousands of years and where drift may have occurred, show wide deviations from the normal gene frequencies. In contrast, most of the blood group gene frequencies over wide areas, such as the whole of northern and central Europe, tend toward uniformity (43). It is possible, on the other hand, that these differences in gene frequencies may have resulted from unknown selective forces and from differences retained after the disappearance of the selective factor.

MATERNAL-FETAL INCOMPATIBILITY

In the assumed stability of the blood group genes, the blood group antigens might have served as excellent tools for tracing relationships among the different races of man. The first, and still the strongest easily demonstrable evidence against this view of their neutral selective value was provided in 1940–41, only about 25 years ago, by Philip Levine and his associates when they showed that hemolytic disease of the newborn was caused by immunization of the mother by fetal antigens that she lacked, but which the fetus had inherited from the father. The Rho (D) antigen is the most frequent cause of the disease in its severe form, even when taking into account the relative frequencies of incompatible pregnancies. Hemolytic disease of the newborn due to Rh_o (D) incompatibility has a maximal incidence of between 1 in 150 and 1 in 200 of all births. About 60% of the infants are sufficiently affected to require exchange transfusion. Consequently, about 1 in 300 of all newborn infants has a degree of hemolytic disease due to anti-Rh_o (D) which requires therapy.

In addition, incompatibilities of other antigens within the rhesus system may occur between mother and fetus. In a series of 2,274 mothers who delivered infants with hemolytic disease, anti-D (with or without anti-C or anti-E), however, was responsible for 99% of the cases (65). The remaining sera contained anti-E, anti-c, or anti-C.

ABO blood group incompatibility undoubtedly also causes hemolytic disease of the newborn, but its extent is not clear. Certain authors (42) have claimed that the disease due to incompatibility within the ABO system is at least as frequent as disease caused by incompatibility within the Rh system. On the other hand, severe cases are so rare that many observers have doubted that ABO incompatibility could be responsible for hemolytic disease of the newborn. Various reasons, including the neutralization of incompatible anti-A or anti-B agglutinins crossing the placental barrier by group-specific substances in the fetal plasma and the lack of sensitivity of erythrocytes of some fetuses toward the incompatible agglutinins, have been suggested for the relative safety of the infant (64). Based upon the number of infants developing jaundice, ABO incompatibility has an incidence of one in 150 births. Other infants may never develop jaundice, although a mild hemolytic process takes place. Yet, only about one in 3,000 of all newborn infants requires treatment for hemolytic disease of the newborn on the basis of ABO incompatibility, in contrast to the 10-fold greater need for therapy on the basis of Rho (D) incompatibility (42). Those infants affected with ABO hemolytic disease are usually group A (subtype A_1, not A_2) or B, secretors of their particular group, and have mothers of group O. The immunizing stimulus appears to be a transfer of blood group substance in soluble form rather than a fetal-maternal transfusion containing red blood cells (33). Thus, selection will affect not only the ABO blood groups but also the secretor character.

In addition to the direct clinical evidence, there is also a mass of controversial statistical data on the effects of ABO incompatibility between mother and fetus on reproductive capacity. In 1957, Edwards (13) concluded that there has not been any satisfactory demonstration within reasonable confidence limits of differences in fertility or sex ratio primarily related to the ABO blood groups. There is little doubt now, however, that loss of A or B offspring of group O mothers may occur at all stages of fetal development. Whereas hemolytic disease of the newborn may result from incompatibilities in both the ABO and Rh systems, early fetal death or eventual sterility is attributable chiefly to ABO incompatibility, and late fetal death or early neonatal morbidity is observed largely as a consequence of Rh system incompatibility. Chung and Morton (5), for example, have calculated that the effect of ABO incompatibility is to "kill about 2 percent of all zygotes" and that "few loci can be as important causes of fetal death as the ABO system."

A recent report by Matsunaga (39) has indicated a significant elimination of zygotes associated with ABO incompatibility in both white and Japanese populations. About 10% of such zygotes were lost in the former, and the figure varied from 3 to 21% in the latter, the lower figure being obtained from a population living under more favorable conditions. Despite the fact that ABO hemolytic disease occurs primarily in mothers of group O, the overall effect of maternal-fetal incompatibility is the same whether the mother belongs to group O, A, or B (21). Analysis of family data suggests that prezygotic selection in favor of group O sperm may be operative. Several hypotheses have been advanced to account for this observation. A sperm carrying the A or B gene may be eliminated because it is destroyed or rendered ineffective when in contact with the anti-A or anti-B in the cervical secretions of a group O mother. It should be noted, however, that it is not yet established whether the genes of haploid sperm cells express themselves with regard to the production of blood group antigens on their surface. In addition to sperm incompatibility, other mechanisms may contribute to the results, as, for example, the unequal production of germ cells carrying different alleles in heterozygous parents. Another possibility, which occurs independently of female genotypes, is sperm competition or the differential survival of sperms of different genotype. Provided that the ABO polymorphism in the world population is stable, there must be selective mechanisms counterbalancing the effects of immunological incompatibility that stabilize the polymorphic state. Several investigators (5, 39) have suggested that the balanced polymorphism is maintained by the advantage of heterozygotes over homozygotes, although the reasons for such an advantage are obscure. An interesting model in which a stable polymorphic state may be maintained without heterosis has been recently suggested (21). Genes favored by prezygotic selection, such as the O gene, may not be favored by postzygotic selection due to the reduced viability of the homozygous carrier. Thus, stable polymorphic states in the ABO and other blood group systems may be maintained by selection pressure operating in the opposite direction in the pre- and postzygotic stages. Additional data and critical analysis of the whole problem, however, are sorely needed.

Several studies have shown that ABO incompatibility increases the risk of abortion (33). A comprehensive study by Wren and Vos (69) indicated an increase in abortion among couples

where incompatibility exists, that is, where the husband's red cells contain A or B antigens not demonstrable in his wife. Of their 122 cases of spontaneous abortion, 45% had incompatible blood group matings as compared with 30% in their control group of 100 couples, each of whom had at least two children without an abortion. Of the 122 mothers in the above series, 59% possessed hemolysins for selected group O red cells in their sera compared with only 7% in the control group. Most of the hemolysins were found in the incompatible mating group of aborters, but there were sufficient numbers in the compatible abortion group to suggest that hemolytic systems unrelated to the ABO groups may be responsible for spontaneous abortions. The hemolysins which are not related to the ABO blood group system showed a frequency of 18% in the abort series compared with 3% in the control group, and they have been identified subsequently as having anti-Tj^a-like specificity (67).

This hemolysin differs from classical anti-Tj^a produced by Tj (a−) individuals in several respects. It does not agglutinate untreated or trypsin-treated cells, nor does it sensitize them to antiglobulin reagents. It is produced by Tj (a+) individuals, acts on the patient's own red cells in vitro, and disappears and reappears in the blood at unpredictable intervals. It has been detected only in Western Australia and has not been found in similar aborter series from several areas of the United States and Canada. Obviously, this hemolysin requires further characterization and study.

Finally, a reciprocal relationship was claimed between the presence of hemolysins and the level of chorionic gonadotrophins. In most of the 56 habitual aborters tested, when the gonadotrophin level fell, hemolysins appeared and remained until an abortion occurred or the gonadotrophin levels rose. When the gonadotrophin level was high, no hemolysins were detected.

In addition to the antigens of the ABO and rhesus systems discussed above, hemolytic disease of the newborn may be caused occasionally by antibodies against other blood group antigens. Cases caused by anti-Kell are the most prominent of these. Powerful selective forces, unrelated to hemolytic diseases of the newborn, have been attributed to the MN system, since there are considerable data that indicate an excess of MN children from matings between heterozygotes. If this excess of the MN phenotype is real, it would indicate a selection in favor of the heterozygote likely to maintain the polymorphism (21, 55). In chickens, similarly, heterozygotes for some of the genes controlling the blood groups may possess an advantage (16).

Blood group incompatibility is a necessary prerequisite for hemolytic disease, but other unknown circumstances also contribute to its incidence. Thus, only about 1 in 10 Rho (D)-negative women after six or more pregnancies with Rho (D)-positive fetuses becomes sensitized (45). Nevertheless, although modern techniques of exchange transfusion may lessen the selective pressures, it would seem that the proportion of Rho (D)-positive and Rho (D)-negative must be constantly changing owing to the selection against the heterozygote exerted by hemolytic disease of the newborn. Such adverse selection would tend to bring to a very low level the rarer Rho(D)-negative gene. The situation may not be so simple, however, since the heterozygote may possess unknown advantages, counterbalancing its disadvantages. In addition, stillbirths and neonatal deaths seem to be a stimulus to replace the lost children, and mothers of children with hemolytic disease, whose husbands are heterozygous, may eventually produce more than their share of Rho (D)-negative children (55). This cannot be the whole explanation for the persistence of both genes, because it can be shown mathematically that such a compensatory effect is not likely to produce a stable polymorphism. There is also the possibility that in primitive populations a reduction in the number of children because of deaths caused by hemolytic disease of the newborn would leave more food for the rest. Under conditions of famine, therefore, the mean number of children reaching maturity in small families would be greater than that in large families. This sort of effect has occurred in birds (32), but it is a highly speculative explanation in man.

A further interesting complication is the influence of other blood groups on Rho (D) and other incompatibilities. It was observed by Levine (34) in 1943 that mothers of children afflicted with hemolytic disease resulting from Rho (D) incompatibility showed a higher than expected frequency of compatibility in the ABO system. Thus, ABO incompatibility, which itself is an important cause of fetal death, may decrease infant mortality in Rho (D)-sensitized women by reducing the incidence of hemolytic disease of the newborn in these women. The most likely explanation for this phenomenon is that ABO incompatible fetal red cells carrying the Rho (D) antigen are removed in the liver by virtue of their reaction with maternal anti-A or anti-B. They are thereby prevented from reaching the sites of antibody formation. Finally, the intriguing possibility that immunological tolerance may play a part in Rho (D) immunization has not been supported by the available data. Immunological tolerance or unresponsiveness to an antigen

results from the exposure of an organism to that antigen sufficiently early in its development. Assuming that maternal blood group antigens as well as antibodies can reach the fetus, children should not be good antibody producers to their mothers' antigens. An Rho (D)-negative child of an Rho (D)-positive mother should not be able to form anti-Rho (D), whereas an Rho (D)-negative child of an Rho (D)-negative mother should be able to do so. Thus, one would have expected a greater incidence of Rho (D)-negativity among the maternal grandmothers of children suffering from hemolytic disease of the newborn. However, this did not prove to be true (51). There is recent evidence, on the contrary, that exposure in utero to the Rho (D) antigen may result in increased antibody formation against that antigen in later life (62). Similarly, the variation in the levels of naturally occurring anti-A and anti-B in different individuals has not correlated with the maternal blood group (30). These results are compatible with more recent findings that immunological unresponsiveness requires the persistence of antigen (41).

Hemolytic disease of the newborn as a result of maternal-fetal blood group incompatibility has been represented by Goodman (19) as an example of his general thesis that the maternal immunological attack on the fetus functions as a selective agent ultimately responsible for the development of certain antigenic patterns in the individual. As a result of the selective action of the maternal immunological system, genes which act during prenatal development would tend to be retained in the homozygous state in the human population, and, alternatively, genes which act primarily during postnatal development and therefore are not subject to this selective pressure would exhibit a relatively high incidence of heterozygosity. In support of this theory is the fact that albumin arises early in embryo-genesis, whereas γ-globulin appears and shows a succession of changes only during postnatal development. Accordingly, antigenic differences between the albumin of man, gibbon, and chimpanzee have not been detectable, whereas human γ-globulin has been distinguished from its counterparts in in the gibbon and chimpanzee. Relating this concept to the blood groups and assuming that the blood group polymorphisms reflect beneficial combinations of heterozygous genes, there will be added advantage to those genes which fail to express their information strongly in prenatal development and thereby escape the selective pressure exerted by the maternal immunological system. In support of this view, Goodman cites evidence that the A and H antigens of human red cells undergo a further succession of changes after birth. Other workers (9) have found also that during fetal life the A and B antigens are weaker in absorptive power than those of adult cells and qualitatively different in that they lack some of the antigenic groupings found in the adult spectrum, including that for A_1. Although compatible with the fact that hemolytic disease of the newborn, attributable to ABO incompatibility, is very often mild, the significance of, as well as the biochemical genetic basis for, the incomplete development of the A antigen until after birth remains to be determined. As far as the Rho (D) situation is concerned, for each Rho (D)-positive gene lost from the population due to erythroblastosis, an Rh-negative gene will also be lost since only heterozygotes are affected. The genes present in the population at the lower frequency (less than 0.5) will be the ones reduced by the iso-immune process to an even lower frequency. Goodman believes that we have to assume that the heterozygous condition offers some advantages which balance the effects of erythroblastosis, thus acting to maintain the Rho (D) polymorphism. His theory predicts that, in the distant future, the human population might still show an Rho (D) polymorphism with the Rh-negative gene showing a good frequency in the population. There would be a marked ontogenetic delay, however, in the expression of the Rho (D)-positive genes, so that the possibility of transplacental immunization to the Rho (D)-positive antigen would be effectively circumvented.

Several investigators have concluded that embryonic injuries and deaths due to iso-immunization by protein antigens, distinct from the blood group antigens, must also be of common occurrence. Recent experimental findings bear on this prediction. When BALB/c female mice were immunized with γ-globulin of C57BL/6 mice and then mated with males of this strain, a high incidence of maternal and fetal deaths was observed (35). Provided that microbial infection can be excluded as the cause of death, additional evidence for an important role of the maternal immunological system in the selection of antigenic variants may be forthcoming.

DISEASES OF THE GASTROINTESTINAL TRACT

Voluminous evidence exists for an association between the ABO blood groups and diseases involving, directly or indirectly, the upper part of the gastrointestinal tract. In individuals who are secretors, substances with ABH(O) specificity are present in high concentration in this region of the intestine. An early report which considered the possibility of a relationship between the ABO blood group system and disease was published

from the Mayo Clinic in 1921 (2). Although 2,446 patients with a variety of diseases were considered, it was concluded that no significant association existed between the two. Yet, in retrospect, the data provide some suggestion for two relationships now believed to exist: a correlation between group O and duodenal ulcer, and between group A and pernicious anemia. Little progress was made for over 30 years, but there are now data in support of these and other associations. In 12 different medical centers as far removed from each other as Vienna and Tokyo and embracing populations in which the blood group distributions are quite different, persons of blood group O were found more likely to develop duodenal ulcer than persons belonging to the other ABO groups. In Tokyo, blood group O individuals were 66% more likely to develop the disease, while in Glasgow the difference was only 17%. Hence, the significance of the association was substantiated at all the centers, achieving statistical significance ($P < 0.05$) in 9 of the 12 locations. It was found also that nonsecretors of the ABH(O) substances were 50% more likely to develop duodenal ulcers than were secretors. If the blood group and secretor status are considered together, it is found that individuals who are both group O and nonsecretors are about 2.5 times more likely to develop the disease than the least susceptible group, that is, those who are secretors of group A, B, or O (6). The reason for this association is not clear, but it may be significant that nonsecretors of the ABH(O) substances usually secrete a mucopolysaccharide molecule of Le^a specificity rather than that of ABH(O) specificity. The association may depend, therefore, upon the serological specificity of the substances in the secretions. Using Coombs mixed cell agglutination and fluorescein-labeled antibodies, Selsnick (54) found that the duodenal cells from secretors contain the corresponding antigen on their brush border, whereas cells from nonsecretors do not. In other parts of the body (skin, buccal mucous membrane, kidney), however, the ABH(O) antigens are detectable regardless of the secretor status. Commenting on the possible significance of the secretor state, Cain (3) pointed out that plant lectins which possess anti-A or anti-B specificity may damage the duodenal mucosa in nonsecretors but not in secretors, presumably because of their neutralization by the antigens. Gastric ulcer is also more common in group O individuals (11). However, the association between blood group O and gastric ulcer is not as strong, although individuals of that group are almost 20% more likely to develop the disease. The other striking association is that between blood group A and cancer of the stomach; persons of group A are about 20% more likely to develop this disease than persons of groups O and B. In addition, people of group A are about 25% more likely to develop pernicious anemia than people of groups O and B (51). There are data indicating further associations, but they are at present only suggestive and require further work before they may be accepted.

The explanation of these statistical correlations is not known at this time. One possibility is that the relationships which have been observed reflect racial or socioeconomic differences in the population, and that the blood group differences are merely secondary. In the case of the correlation between nonsecretion and the prevalence of duodenal ulcer, this has been proved quite unlikely, for the subjects who are nonsecretors are more susceptible than their sibs who are secretors (8). By using healthy brothers and sisters of patients as controls, the contribution of both genetic and nongenetic factors may be more readily ascertained. This type of analysis needs to be extended.

The genetic significance of the blood group and disease associations resides in their potential importance, through selection, to the ultimate genetic constitution of man. Since several of the diseases considered are rare or of late onset, it is difficult to believe that they have had a marked effect on the world-wide distribution of the ABO blood groups. Duodenal ulcer is a disease of adulthood and should not interfere appreciably with reproduction. Nevertheless, second order effects of these associations may be postulated and, although not very great, a certain degree of selective pressure must necessarily have been exerted. It should be noted, however, that there is every indication of a balanced polymorphism in the blood groups, maintained by unknown mechanisms. Even very large series do not show differences in longevity among blood donors belonging to the different ABO groups (52). Generally, geneticists do not suppose that any trait is completely neutral as far as selection is concerned. The ability to taste phenylthiocarbamide (PTC) was at first regarded as a variation which could hardly confer any selective advantage, since this compound is not found in nature. Yet, suggestions for an association between PTC taster ability and certain thyroid diseases (14, 31) have been strengthened by a recent report (1) that goiter in a nontaster is more likely to evolve into the nodular form, but, in a taster, into a diffuse hyperplasia.

The genetic basis for the observed associations is far from understood, but it is obvious that we are not dealing with an inherited disease arising

from a single gene mutation, such as in sickle cell anemia or fibrocystic disease of the pancreas. Those individuals who are nonsecretors and of blood group O frequently exhibit an elevated incidence of duodenal ulcers, but they certainly are not the only persons who suffer from this condition. In addition to environmental influences, which might be assessed by studying sibs and adopted children in families, there are certainly other genes involved. Such multifactorial inheritance implies that the underlying genetic basis of duodenal ulceration may give rise to a continuous range of variation in susceptibility. This circumstance leads to difficulties in analysis, since we are generally dealing only with those who have and those who do not have a particular disease, and usually we cannot determine the degree of susceptibility of those free from the disease. The blood group associations seem to suggest, in any event, that the genetic element in ulceration is multifactorial.

RHEUMATIC FEVER

The pathogenesis of rheumatic fever has not been completely elucidated, although there is little doubt that infection with the group A hemolytic streptococcus is essential to trigger the attack. Only a small proportion of cases of streptococcal tonsillitis, however, develop the complication. Glynn and Holborow (17) have pointed out that the activity of the streptococcus in the throat might be affected by the blood group secretor status of the host. Furthermore, the ability of streptococci to adsorb haptenic polysaccharides and convert them to complete antigens suggested the possibility that a similar sequence of events might be established as a result of streptococcal throat infection. These considerations led them to investigate the secretor character in patients with rheumatic fever. The results obtained by these and other investigators (7, 17) indicated that there is a significantly increased incidence of the disease in nonsecretors and in those who are not group O. It was postulated by Glynn and Holborow (17) that rheumatic fever might develop only in those individuals who are homozygous or heterozygous for the nonsecretor gene. This hypothesis has been retracted recently, since rheumatic fever has been found to occur in homozygous secretors (27). Nonetheless, the distribution of the secretor genotype in rheumatic fever patients differed from normal in that these patients showed a lower frequency of homozygous secretors. Thus, it has been postulated by Kaklamanis, Holborow, and Glynn (27) that the observed association may be explained if the substance in the throat secretions influencing susceptibility to rheumatic fever is an intermediate in the synthetic pathway between precursor and H substance. As this synthesis is controlled by secretor genes, it would be expected that the conversion of this intermediate is inhibited in the homozygotic nonsecretor. The accumulation of this compound thereby would enhance susceptibility to rheumatic fever. The experimental basis of this hypothesis has been challenged recently, however, by Dublin et al. (12). These investigators analyzed the secretor phenotypes of the offspring of rheumatic secretor and nonrheumatic nonsecretor parents. The results did not indicate a deficiency of homozygous secretors among rheumatic parents. Even if the nonsecretor status did contribute to rheumatic fever susceptibility, there is evidence to suggest that it is not a predominant factor. Environmental conditions affecting the spread of streptococci are undoubtedly of prime significance. Nonsecretors are extremely rare among North American Indians, but data obtained from Selective Service examinations indicate that rheumatic fever may be less common among certain Indians than among the rest of the U.S. population (18). Additional studies are needed to correlate the secretor status of Indians with rheumatic fever. Finally, findings of an antigenic similarity between cardiac tissue and streptococcal membranes (28, 70) are of interest and obvious significance as an approach to the role of streptococcal infection in the induction of autoimmunity in the nonsuppurative sequelae, rheumatic fever and glomerulonephritis. In the absence of any significant antigenic relationship between the streptococci and the blood group antigens, however, the bearing of the cross-reactivity between the streptococci and heart tissue on the secretor status of an individual and susceptibility to rheumatic fever remains uncertain.

POLIOMYELITIS

A careful series of studies by Jungeblut and his associates (24) was designed to examine the frequency of paralytic poliomyelitis among individuals of different blood groups. The worldwide incidence of clinical poliomyelitis, as distinguished from infection without paralysis, was claimed to diminish in direct proportion to the increase of blood group B. The percentage of blood group B individuals among East European and Asiatic races living in northern latitudes, presumably relatively free from the disease, varies from 20 to 34%, in contrast to about 9% among the white population of the U.S. (43, 68). This study concluded that paralytic poliomyelitis selects individuals with blood group O or A_2 or nonsecretors less frequently than these groups occur in the normal populations. The differences

were not large, and none of the individual paralytic poliomyelitis series showed a statistically significant difference in the frequency of occurrence of any single blood group as compared with the corresponding control series. Nevertheless, these small differences were considered significant in view of their consistency in the different series and because of the very large numbers involved. The incidence of the Rho (D) antigen differed very little between the patients and the normal control subjects.

An attempt to determine the basis for the varying susceptibility of individuals of different blood groups was made by the neutralization test, involving the inoculation of poliomyelitis virus into monkeys, with 26 human convalescent sera (25). The results indicated that six of seven sera of group B individuals were capable of neutralizing the virus, but not more than half of the sera belonging to groups O and A neutralized the virus. The removal of anti-A from the sera of the group B individuals, however, did not result in loss of neutralizing power, so that the basis for the increased neutralizing activity of group B sera was not identified. With the discovery of the growth of poliovirus in cultivated cells in vitro and the consequent relative simplicity of neutralization tests, this problem might be re-examined.

In the present state of knowledge, it would seem fair to conclude that the comparative freedom from paralytic poliomyelitis in Asia and the high incidence of blood group B in Asiatics may be fortuitous and of little consequence. Jungeblut and Smith (25) recognized, moreover, that North American Indians and Eskimos who show a high incidence of group O and practically no group B have enjoyed the same freedom from the disease. Poliomyelitis in its worst epidemics cannot be compared in its harmful effects to plague, typhus fever, yellow fever, malaria, and smallpox. It is doubtful, therefore, that poliomyelitis has been the agent responsible for the prevalence of the B gene in certain areas of the world. The association between resistance to poliomyelitis and blood group B could have resulted from the fact that exposure to the virus in infancy tends to result in subclinical infections, so that virtually all children, in areas where standards of sanitation are not high and where blood group B happens to be of high incidence, are immune to paralytic poliomyelitis.

BRONCHOPNEUMONIA

A significant study by Struthers (61) was designed to elucidate findings by other investigators indicating that there were fewer group A children surviving in AO families (father group A, mother group O) than in OA families (father group O, mother group A). Very few of the "missing" children apparently died of hemolytic disease, so seemingly some of the observed deficiency of group A children may have arisen after birth. By the use of postmortem blood samples, the ABO groups of a consecutive series of 400 West Scottish infants and children autopsied in Glasgow were compared with those of the adult population to which the parents belong. A highly significant deficiency of group O (i.e., an excess of groups A, B, and AB) was found in the series, particularly among the infants with autopsy evidence of bronchopneumonia. In 55 cases with no apparent abnormality other than bronchopneumonia at autopsy, the frequency of group O was as low as 25.5%, as against 50% for the cases without bronchopneumonia ($P < 0.001$). Struthers postulated that the maternal antibodies may diminish the resistance of heterozygous offspring to certain infections. In this context, it is noteworthy that some of the cases undoubtedly were of pneumococcal origin and that there is a known antigenic relationship between pneumococcus type XIV polysaccharide and the blood group substances (26). As an alternative possibility, Struthers suggested that antibody sensitization of red cells may lead to effects within the pulmonary circulation predisposing to certain local infections. To account for the deficiency of group O in cases of bronchopneumonia, these theories are vague in the absence of more definitive information. It will prove difficult, of course, to repeat the analysis that Struthers has made because of the widespread use of antibiotics. However, pneumococcal infections still occur at a significant frequency in the tropics, and the incidence of these infections in relation to blood group constitution would be worth reinvestigating. The findings of Struthers in Glasgow were not confirmed in a slightly larger series reported from London by Carter and Heslop (4). The latter investigators were able to confirm the deficiency of group O, but few of their patients had pneumococcal infections, the pneumonia always being a "secondary" development. It is possible, therefore, that their cases were not strictly comparable to those reported by Struthers.

COMMON ANTIGENIC DETERMINANTS BETWEEN BLOOD GROUP SUBSTANCES AND MICROBIAL AGENTS OF DISEASE

Plague and Smallpox

If microbial agents of disease possessed antigenic determinants common to those of the blood group substances, one would have a rational

basis for the possibility that different blood groups may correlate with greater resistance or susceptibility to different disease agents. Assuming that an infecting microbe possessed blood group A activity, then the naturally occurring anti-A individuals of blood groups B and O might contribute to host defense mechanisms against this microbe. Moreover, individuals of blood groups A or AB may not only be more vulnerable initially to this particular microbial agent, but, in accord with the concept of *horror autotoxicus*, their antibody production against the determinants common to the blood group substance and invading microbe might be suppressed. If it were found that the current incidence of individuals of blood group A was lower in those areas of the world where devastating smallpox epidemics had occurred, one might postulate that the possession of blood group A specificity constitutes a selective disadvantage in such populations. Of course, one must make an additional and questionable assumption, for which there is no direct evidence, namely, that the blood group distribution in the affected populations was different prior to the epidemics. In accordance with these views, evidence has been marshalled by Vogel, Pettenkofer, and Helmbold (66) which led them to suggest several correlations involving the blood group substances and the incidence of plague and smallpox.

Pasteurella pestis has been claimed to possess an antigen which is very similar to the H antigen of the ABO(H) system in its reaction with rabbit antiserum. Patients of blood group O, because of their presumed inability to produce anti-H, fared poorly in plague epidemics. In accord with this concept, gene O is now very frequent in places where few or no plague epidemics have occurred, but its incidence is low in the ancient plague centers of Mongolia, the Orient (Turkey), and North Africa (lower Egypt).

The experimental findings upon which these statements are based have been questioned by Springer and Wiener (58). First of all, with three different strains of *P. pestis* grown on defined medium devoid of blood group activity, two manifested no blood group activity and the other only traces of both H and B specificities. Moreover, this finding is consistent with failure to find the monosaccharides believed to be responsible for blood group H(O), B, or A specificity in several different strains of the plague bacillus. Since the strains responsible for the old epidemics are not available, there is no information concerning their antigenic structure. Finally, individuals of groups A, B, or AB, except for the very rare Bombay phenotypes, are not devoid of H substance, but merely possess less of this antigen, and individuals of groups A, B, or AB generally do not possess the capacity of forming anti-H, particularly of the type active at 37 C.

Based upon the production of anti-A in rabbits injected with vaccinia virus grown in the chorioallantoic membrane of the chick embryo, the smallpox virus has been assumed to possess an antigen which is very similar to the A antigen of the ABO system. Thus, humoral resistance against smallpox may be more effective in patients of blood groups B and O, who carry anti-A in their plasma, than in persons of type A or AB. The Asian and African distribution of the A gene supports the theory of a selective disadvantage among individuals carrying this gene who are infected with smallpox virus. This holds true especially for India, Arabia, and tropical Africa, where smallpox has had devastating effects and where the frequency of the gene for blood group A is relatively low. Therefore, in areas with smallpox as well as plague, such as Mongolia, China, India, and parts of Russia, the relative frequency of the B gene would increase owing to selection against the A as well as the O genes.

Similar to the situation with plague, cogent and serious objections have been raised against the hypothesis that selective pressures have been exerted by smallpox against individuals possessing the A gene. First of all, there is no evidence that the vaccinia virus can be completely equated antigenically with the variola (smallpox) virus. Secondly, there is excellent evidence that the A activity ascribed to the vaccinia virus was probably derived from the chick embryo, since A substance has been found in uninoculated chorioallantoic membranes of chicken eggs (57). Furthermore, no increase in anti-A titer has been found in rabbits immunized with vaccinia virus preparations obtained from infected rabbits. Rabbit anti-A serum exerts no inhibition upon the growth of vaccinia virus in the chorioallantoic membrane of the chick embryo. Moreover, the incidence of smallpox reported recently from Brazil and Nigeria has been unrelated to the ABO blood groups of the patients (1). Nonetheless, other reports claim a higher incidence of smallpox scars among group A individuals in India and Pakistan, and greater than expected postvaccination reactions, including encephalitis, among group A subjects in Germany (49). Finally, in the unlikely event that variola virus does contain A substance, there is still no convincing evidence that humoral antibody in general, or anti-A in particular, plays a significant role in recovery from viral infection (15), although it may play a prominent part in prophylaxis.

Myxoviruses

Vaccination with egg-grown influenza virus has been shown to produce increased levels of anti-A in human subjects. Most likely, this is the result of contamination of the virus preparation by blood group active mucopolysaccharides originally present in the uninfected embryonated chicken eggs (57). One should be cognizant, therefore, of the potential hazards in immunizing women in the child-bearing age with such vaccines, since there is a possibility of ABO immunization and subsequent hemolytic disease of the newborn. This is particularly true for women of group O and possibly B, although there are no reports available indicating that such immunization has led to hemolytic disease of the newborn (38). ABO immunization may exert its effect, however, early in fetal life to produce abortion and miscarriage. Marked blood group activity has been found to be associated with other myxoviruses. Isaacson and Holden (22) found that chimpanzees infected with DA virus, a member of the SV-5 group of myxoviruses, showed marked rises in anti-B titers.

Enteric Bacteria

Infections by these organisms still produce a high mortality today, especially among young children, in many underdeveloped areas of the world. Endemic diseases of this kind, acting on many generations, may have produced selection at least as significant as that produced by the great epidemics. The unequivocal demonstration of blood group antigenic activity among many strains of the *Enterobacteriaceae* by Springer, Williamson, and Brandes (60) has led naturally to speculation that infections by these organisms might produce selection based at least partly upon the blood group distribution within a population. There is little evidence to substantiate this view. Undoubtedly, however, enteric infections could provide the antigenic stimulus for the production of some of the "naturally" occurring isoantibodies.

Springer and his co-workers selected 282 gram-negative, smooth strains consisting mainly of organisms isolated from blood cultures and having known somatic (O) antigens. Of these, 10% showed high blood group substance activity, but it was felt that a random selection of strains of enteric bacteria would have yielded a lower figure (59). High activity was noted only for group B and H (O) substance; no bacteria having high A activity were found. Also lacking were bacteria with M, N, and Rho(D) activity, a finding which is compatible with the rare occurrence of agglutinins against these antigens in the absence of known prior immunization. Of the few gram-positive bacteria tested, none showed A, B, or H (O) activity.

The presence of the known monosaccharide precursors of the human blood group substances related well with the blood group activity of the strains. The H (O) active bacteria contained fucose, A active bacteria contained *N*-acetylgalactosamine, and B active bacteria contained galactose. While significant blood group substance activity has not been observed in bacteria whose somatic antigens lack the monosaccharide primarily responsible for this activity in the human blood group mucopolysaccharides, the converse is not necessarily the case. For example, strains containing high levels of fucose, such as *Arizona* 21 and *Escherichia coli* O86:B7, show practically no H (O) activity. Fucose was found in all O antigens of the highly active bacteria irrespective of their blood group specificity. Blood group activity showed no apparent relationship to pathogenicity; among highly active bacteria, both pathogens and nonpathogens were found. Included among those strains without blood group activity were five strains of *Shigella flexneri*.

Any selective effect exerted via the blood groups would result presumably from the action of anti-A or anti-B, or both, upon the particular bacterium involved. To determine the validity of this suggestion, *E. coli* O86 possessing B substance specificity was selected for testing (40). This strain has the greatest blood group antigenic activity of any known bacterium, about 10 times greater than that of the second ranking *Arizona* O21 which also has group B activity. The bactericidal activity of pools of fresh normal human sera from individuals of different blood groups showed no significant differences when tested against *E. coli* O86, although the mean bactericidal antibody titer against this organism in the sera of five mothers of group O who gave birth to B babies was 6.3, in contrast to a mean titer of 2.7 obtained with the sera of three mothers after homospecific pregnancies. Additional studies indicate that the B reactive grouping is involved in the human serum bactericidal reaction against *E. coli* O86, but that it is an insignificant component in the reaction of an antiserum against *E. coli* O86 which is directed against the entire antigenic mosaic of the organism. Moreover, absorption and removal of anti-B from *E. coli* O86 antisera resulted in no detectable agglutinin loss and extremely slight loss in bactericidal antibody against *E. coli* O86. Thus, even with the microorganism having the most potent blood

group activity so far detected, there is little or no experimental or epidemiological evidence incriminating the blood groups as a selective force in diseases caused by the enteric bacteria.

The concept that an antigenic relationship of host and parasite may play an important part in determining host susceptibility to infection has not been restricted to the blood group antigens of man. The peculiar susceptibility of the mouse to *Salmonella typhimurium* may conceivably result from the possession of a common antigen in the tissues of the susceptible host and *S. typhimurium* (23). Pig serum, which displayed considerable opsonic activity against the virulent C5 *S. typhimurium* strain, also gave rise to anaphylaxis in the mouse when injected intravenously (53). Results have been obtained suggesting an antigenic relationship between Rous sarcoma virus and the chicken. Turkeys, which are normally resistant to Rous sarcoma virus, could be made susceptible if injected during embryonic life with blood cells from the chicken, which is the susceptible host to the virus. Blood from different strains of fowl, pigeon blood, and guinea pig and sheep erythrocytes were all active in eliciting susceptibility in this fashion, whereas rat and human group O cells were not (20).

As implied previously in considering rheumatic fever, the possession of common antigenic determinants between mammalian tissues and microbial agents of disease may elicit autoimmune antibodies. Also, an antigenic similarity has been demonstrated between group A streptococci, which gives rise to glomerulonephritis in the rat, and that animal's glomerulus (37). Sometimes individuals who are immunologically competent in most respects seem to lack the ability to respond to a specific agent. Patients with generalized vaccinia gangrenosum do not possess circulating antibody against vaccinia virus despite normal amounts of γ-globulin (29), and children apparently immunologically competent who have suffered from numerous recurrent staphylococcal infections lack antibodies which inhibit the Müller phenomenon (50). One might speculate that such individuals share an antigenic determinant with the particular parasite that is lacking in normal individuals.

MYXOVIRUSES

The possibility that the inheritance of any natural resistance to acute respiratory diseases of viral etiology might be related to the blood groups was considered recently by McDonald and Zuckerman (40). They analyzed the distribution of ABO and Rho(D) blood groups among nearly 2,000 Royal Air Force recruits in three different locations who had been admitted to sick quarters with viral respiratory infection, diagnosed by virus isolation or by a minimal fourfold rise in antibody titer. The blood group distribution in a sample of over 47,000 uninfected Royal Air Force recruits served as a control. The incidence of influenza A1, influenza B, and coxsackie A21 (Coe virus) infections among the different blood groups did not differ greatly from expectation. However, there was a considerable excess of group O patients and a corresponding deficiency of group A among the subjects with influenza A2 infection, whereas the adenovirus group showed an opposite trend. For influenza A2, the difference was highly significant ($P < 0.00001$) and for the adenovirus infection it was moderately so ($P < 0.005$). The proportion of Rho (D)-negative patients in each diagnostic category showed only minor variations. These results are noteworthy because acute viral respiratory infections, with secondary bacterial complications, are responsible for many early deaths before the end of reproductive life. Under such circumstances, some selection for the more fit genotypes with respect to blood group distribution may well occur.

The basis for the enhanced resistance of blood group A individuals to influenza A2 virus is not known. Whether it involves antibody or an inhibition of the virus by A substance in respiratory-tract secretions or on cell surfaces is dubious. There is no experimental evidence that the A2 strain shows any undue susceptibility to inhibition of its hemagglutinating activity by A substance. Because the A2 virus was new to the population and the other viruses were not, the advantage possessed by persons of blood group A against this virus may extend also to other viral agents. Previous exposure to other viral agents may have obscured the possibility of natural resistance of low specificity. A high degree of specificity would suggest an immunological mechanism, but there was no evidence of antibody to A2 virus in the population before 1957, and the detection of this antibody was restricted to persons over 70 years of age. The finding that subjects of group A were, on the contrary, more susceptible to adenovirus infection is equally difficult to explain. A reasonable possibility, suggested by McDonald and Zuckerman, is that these individuals may have failed to become infected and may not have acquired antibody in childhood because of enhanced natural resistance. These significant findings relating differential susceptibility of individuals of different ABO blood groups to respiratory viral infections should be reinvestigated, especially among young children just exposed to adenoviruses.

OTHER INFECTIONS

Many observations, some of a rather tenuous nature, have been made associating blood group activity with many other agents of disease or their products. An attempt will be made to summarize some of these studies. *Rickettsia prowazeki* and *Rickettsia mooseri*, the agents of epidemic and murine typhus, respectively, have been reported to have blood group B activity (63). In view of the high mortality resulting from typhus epidemics and the relatively low incidence of blood group B in Western Europeans, this observation warrants more extensive study from both a genetic and an epidemiological pont of view.

There is indirect evidence that malarial parasites may have blood group antigenic determinants. The sera of patients suffering from repeated attacks of malaria have shown increased anti-A and to a lesser extent elevated anti-B titers as compared with normal individuals or with patients recovering from a single attack (47). It was concluded that malarial parasites have blood group A and B activity, with A activity predominating. Compatible with this finding are other observations, namely, that anti-A exerts a suppressive effect on plasmodia and that group A subjects are more often febrile than subjects of other groups. Hence there is the interesting speculation that malaria may provide one selective factor contributing to the high blood group B frequencies found in Asian and African populations. Along similar lines, one can cite the lower frequencies of Rho (D)-negative individuals found in malarial regions of Italy. It has been suggested that thalassemia and deficiency in glucose-6-phosphate dehydrogenase, both of which are common in malarial regions, may have a synergistic effect on the incidence of hemolytic disease of the newborn resulting from Rho (D) incompatibility, thereby increasing the selective pressure against Rho (D)-negative individuals (1*a*).

Antigens of the helminths have also been found to be related to the blood group substances. These are polysaccharides with A (that part of the A antigen common to A1 and A2) activity and have been detected in *Trichinella spiralis*, *Necator americanus*, *Faciola hepatica*, *Ascaris lumbricoides*, and other helminths (47). Infection of pigs with *Ascaris suum* elicited the formation of anti-A, and preparations of *A. suum* neutralized human anti-A and anti-B but had no effect on anti-Rho (D) (56). In addition, high levels of anti-A were elicited in rabbits infected with *A. lumbricoides*. Another finding of significance is that polysaccharides with blood group A activity, extracted from animal parasites, such as *A. lumbricoides*, may be absorbed onto human red cells of groups O and B. The erythrocytes then acquire A specificity, and may be agglutinated and lysed by natural or induced agglutinins (formed in response to the erythrocyte-polysaccharide complex). Conceivably, the anemia associated with parasitic infections may result, in part, from the production of isoantibodies induced by this means. Finally, it is not known whether any particular blood group in man or animals renders them more susceptible to any parasitic infection. Certain heavy helminth infestations, such as hookworm in children, might affect the mobility of subjects and exert a selective effect, but probably such effects would be quite limited in comparison with those produced by microbial infections.

IMMUNIZABILITY AND THE BLOOD GROUPS

Just as impaired immunological response of a host results when an invading microbe possesses an antigen in common with the host, the presence of a blood group determinant in a vaccine or toxoid may preclude an adequate immune response in individuals of a particular blood group. The disproportionately high blood group A activity associated with the Vi antigen has been instructive in this regard. The Vi antigen of Felix represents the K or capsular antigen of *S. typhosa* and several other enteric bacteria. The significance of the Vi antigen in immunization and protection of rodents against challenge with *S. typhosa* is well documented, although its role in the immune response of man remains unclear (48). Purified Vi antigen was found to be consistently reactive for group A activity, and slight A activity was found in several Vi-containing organisms, including *Salmonella typhosa* strain Ty2, *S. typhosa* strain Vi I, and *Paracolobactrum ballerup* (44). To determine the anti-Vi response of individuals of different blood groups, sera of 204 individuals injected with purified Vi antigen were assayed for Vi hemagglutinin 14 days after injection. Although the geometric mean titer of individuals of groups A and AB was 95 and that of the others was 109, the difference is not significant and does not support the thesis that an individual's blood group may influence his response to a bacterial antigen with blood group activity. In addition, chimpanzees which do not respond as well as man to purified Vi antigen are predominantly of blood group A, but whether there is a causal relationship is conjectural.

An old observation by Nowak (46) that individuals of blood group A show a deficiency of antitoxin production after recovery from diphtheria may have bearing upon the response of different individuals to diphtheria toxoid. He found

that, of 20 such group A individuals, 14 were Schick-positive, but of 30 comparable individuals of group O only 13 were Schick-positive. The numbers are small, and, in the absence of demonstrable blood group A activity in diphtheria toxin, the significance of this finding is obscure.

RESPONSE TO THERAPY

On the basis of statistical analyses of reports for the years 1924–1929 Vogel, Pettenkofer, and Helmhold (66) claim to have established a relation between the course of syphilis and the ABO groups. Susceptibility to the disease was found to be uninfluenced by the blood groups, but patients of group O had a significantly better chance of becoming seronegative as a result of specific therapy than did patients of the other blood groups. In one study of 1,425 cases, twice as many patients of blood group O became seronegative as those of the other groups. The point was made that the present high frequency of group O in Indians of Central and South America might be explained by a more effective resistance by group O individuals against *Treponema pallidum*. There would seem to be no known reason why the Wassermann antibody titer of group O individuals should decline more rapidly than that of individuals of the other blood groups. Although the decline of Wassermann antibody titer has been used as an index of therapeutic efficiency, treponemal immobilizing antibody is undoubtedly of greater significance in resistance than is Wassermann antibody, and it is not known whether immobilizing antibody disappears more rapidly in group O patients. Moreover, if one postulated that the relatively rapid decline of Wassermann antibody titer in group O patients may have contributed to cure and survival, it would be necessary to assume that the drugs in use prior to Ehrlich's discovery acted in a similar fashion. Unfortunately, the distribution of syphilis prior to Columbus' discovery is controversial. The original findings in patients treated with arsenicals cannot be repeated, but animal experimentation is possible, and the variation in response to penicillin therapy among individuals of different blood groups could be easily determined today.

There are examples illustrating clearly the genetic influence on the therapeutic effects of drugs. Isoniazid, which is used in tuberculosis therapy, may be acetylated and inactivated either slowly or rapidly by individuals of different genotypes (10). It is interesting to speculate that fast inactivators might be more susceptible to tuberculosis, particularly since natural tuberulostatic compounds might be rapidly metabolized. Present evidence is totally inadequate, however, to conclude that the pattern of isoniazid inactivation is correlated with susceptibility to tuberculosis.

LINKAGE OF BLOOD GROUP GENES AND DISEASE SYNDROMES

Genes are said to be linked when they are located on the same chromosome. The term linkage refers to the physical association of two or more genes and does not imply that a functional relationship exists between the particular phenotypes designated by the linked genes. For instance, the alleles of the ABO blood group system and the dominant gene determining an abnormality, the nail-patella syndrome, are linked. Yet this does not imply that the nail-patella syndrome is associated more frequently with persons of group O, for example, than with persons of groups A, B, or AB; i.e., the nail-patella syndrome gene may be linked to an O, A, or B gene. Conversely, in the absence of pedigree studies, analysis solely of blood group distribution and correlations with nail-patella syndrome frequency provides no evidence for genetic linkage between the two genes.

In addition to the linkage between the ABO genes and the locus for the nail-patella syndrome, there is a close linkage between the locus for the gene determining elliptocytosis and that of the Rh blood groups. Elliptocytosis is an abnormality of the erythrocytes, a high proportion being of oval shape, but it does not seem to be associated with disability (6).

Genes controlling the formation of the blood group antigens are potentially useful as markers for genetic studies. For instance, if a particular blood group gene were linked with the locus on the X chromosome which determines hemophilia, it would often be possible in a family to distinguish carriers of hemophilia from normal women. A sex-linked blood group antigen carried on the X chromosome was discovered in 1962. It has important applications, as Race and Sanger (51) have indicated, to the mapping of the X chromosome, to the many conditions due to abnormalities of the sex chromosomes, and to the Lyon theory concerning the possible inactivation of one X chromosome in the somatic cells of the normal female. Much has already been accomplished in mapping of the X chromosome. Fortunately, the sex-linked blood group, Xg, is not very close to two other excellent markers on the X chromosome, those for color blindness and the glucose-6-phosphate dehydrogenase deficiency, so that additional mapping of the X chromosome has been possible. Four sex-linked genes can now be put in order as follows: blood group Xg—glucose-6-phosphate - dehydrogenase deficiency — color blindness—hemophilia. Families representing about half of the 60 known X-linked conditions

have been tested, but so far the loci for only two, besides that of glucose-6-phosphate-dehydrogenase deficiency, appear to be within measurable distance of Xg. These are the loci for a very serious disease, angiokeratoma, and for a mild skin condition, X-linked ichthyosis. There is evidence that the latter is near glucose-6-phosphate dehydrogenase deficiency, but the former may be located in either direction from Xg (53*a*).

Use of the blood group marker Xg, together with other X chromosome markers, may provide an indication of the origin of the X chromosome in aneuploid (XO and XXY) individuals, i.e., whether the nondisjunction (one type of chromosomal aberration) of the sex chromosomes which yields individuals of constitution XXY (Klinefelter's syndrome) or XO (Turner's syndrome), is of maternal or paternal origin. Finally, it was hoped that the sex-linked blood group antigen might contribute experimental evidence bearing on the Lyon hypothesis. According to Lyon and several other workers, early in embryogenesis one of the two X chromosomes in each female somatic cell becomes genetically inactive. Although it is presumably a random matter as to which X chromosome in any single cell is the inactive one (36), the hypothesis suggests that the same X chromosome remains inactive in all descendants of that cell. Consequently, one would expect that in the heterozygote, if the X chromosome carrying Xg^a gene happened to be the one inactivated in cells destined to produce most of the marrow, then in later life most of the red cells of that individual would be unagglutinated by anti-Xg^a. In other words, evidence of a red cell mosaicism for the Xg^a antigen in female heterozygotes would support Lyon's theory. Probably because of technical difficulties, including the lack of a sufficiently potent anti-Xg^a serum, and because of other genetic considerations, the results obtained so far have not been useful in confirming Lyon's theory. Mosaicism of the predicted type has been demonstrated, however, for several conditions in heterozygotes, particularly for the glucose-6-phosphate dehydrogenase deficiency trait.

SUMMARY

The antigenic individuality of the red blood cells, and probably of other cells and substances as well, plays a powerful part in certain diseases. Immunization by fetal Rho (D) antigen of Rho (D)-negative mothers and by fetal A or B antigens of group O mothers is known to lead to fetal death, abortion, and hemolytic disease of the heterozygous newborn. In these conditions, the effects of antigenic differences between fetus and mother are clear, although at least one complicating interaction is known. This involves the fact that ABO incompatibility appears to reduce the likelihood of hemolytic disease of the newborn arising from Rho (D) incompatibility. Despite the constant elimination of heterozygotes resulting from maternal-fetal incompatibility, a balanced polymorphism seems to be maintained for reasons not clearly understood.

There is also evidence of several associations between disease of the upper part of the gastrointestinal tract and the ABO blood group and secretor status. The significance of these associations is difficult to assess. One may merely note that, in secretors, substances with ABH(O) and Lewis specificity are present in large amounts in the gastrointestinal tract.

The diseases involved in these associations are those of adults and have not interfered appreciably with reproduction. They have probably not exerted a great effect on the distribution of the ABO blood groups. It has been suggested, however, that differences in the blood groups may be related to resistance to devastating infectious diseases, such as plague and smallpox. This postulate is based upon known or supposed antigenic similarities between the etiological agents and their hosts. It is presumed that the invaded host can readily prepare antibodies against those microorganisms that differ most from its own systemic antigens. This intriguing speculation goes far beyond presently verifiable experimental evidence, and further work in this area is needed.

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