Most humans have on their red blood cells at least one antigen from each of the first nine blood-group families. This is a universal truth of obvious importance, even though its significance is not now apparent. The simplest possibility is that each of the blood group systems provides essential materials for the construction of the red cell envelope, and that the most satisfactory materials are those produced by the common genes. Occasionally persons are encountered who have no detectable antigen of one of the blood group families: the term “minus minus” has been used by Race and Sanger\(^1\) to describe such phenotypes, as well as other phenotypes in which alternative antigens are lacking though other antigens of the system are still present. These rare types are a source of great interest and speculation, both as to their significance and their genetic explanation.

The original “minus minus” phenotype was Landsteiner’s common type O\(^9\), which was long considered as merely the absence of both the known antigens A and B. Then, in 1927, Schiff\(^17\) discovered that type O bloods all had the antigen H, which was interpreted as indicating that the O gene, allelic to A and B, produced antigen H, and type O seemed neatly explained. The genetic interpretation of common type O had to be reconsidered when Levine, et al.,\(^10\) showed that the “Bombay type O” was explainable by the action of genes independent of the ABO genes, a milestone in our comprehension of the complexity of blood groups. Common type O does not, however, except for historical reasons, belong in the company of the other “minus minus” phenotypes as these are defined.

Quite recently, many other “minus minus” phenotypes have been found, and a list is shown in Table 1. The list is now almost complete in the sense that examples of the “minus minus” phenotype have been found in each instance where reciprocally related antigens are known, except for M and N. There is no such phenotype in the Wright, Diego, or Sutter systems because no alternatives to antigens Wra, Dia, and Jsa are known. If Wrb, Di\(b\), and Jsb are found, it can be confidently predicted that types Wr (a\(−\)b\(−\)), Di (a\(−\)b\(−\)), and Js (a\(−\)b\(−\)) will also eventually be found. The important question, however, is the basic nature of these phenotypes. There appear at present to be several mechanisms by which they can be produced.

Four general classifications are shown in Table 1. Type #1, the common type O, has been mentioned. Type #2, the Bombay type, was shown by Levine, et al.,\(^10\) to be caused by the absence of gene X, a gene independent of the ABO genes, which nor-
mally produces H substance or an ABH precursor. Common type O is therefore, possibly, a combined effect of gene X and the absence of any ABO gene. Gene X thus is visualized as producing the basic ABO substance, which may then be modified by A or B genes to produce types other than O.

The nature of type #3 (Table 1) is even less well understood. In these phenotypes there is absence of some, but not all, of the antigens known to belong to the particular system. The type --D-- (C-c-D+E-e-) was originally considered to be caused by a deletion of C genes and E genes. This is still an acceptable possibility. Several other, generally similar, varieties of Rh "minus minus" phenotypes have been reported. In the MN system, the type S-s- is comparable. As with the common type O, it is possible that still undiscovered alternatives to C, E, or S may turn up, but one fact argues against this happening. In all these cases, other "expected antigens" (in my opinion) also are missing. Type --D-- lacks (in addition to C, cE, and e) the antigen Hr, as do also the other "minus minus" phenotypes of the Rh system. Type S-s- lacks also the U antigen; furthermore, the gene that produces M but no S or s also fails to produce any N, whereas other M genes do produce some N antigen.

As Race and Sanger pointed out, another possible explanation of these phenotypes is a small inversion, or translocation, the inverted or misplaced piece, in unfamiliar surroundings, not behaving normally.

In the fourth category of Table 1 are seven types in which the individual may be homozygous for an amorphic (do-nothing) gene. In the Lewis system this amorph would be the gene le of Ceppellini, which fails to produce any identifiable Lewis substance. In the Duffy, Kidd, and Lutheran systems, the "minus minus" phenotypes are tentatively assumed to be due, or possibly due, to homozgyosity for the amorphic genes Fy, Jk, and Lu. The P system is not strictly comparable to the others, because P and Tja have not been proven to be alternative characters; nevertheless, the "minus minus" phenotype is considered to occur in persons homozygous for the amorph p. The Kell type K-k-Kp (a-b-) of Chown, et al., is known to produce also no Ku, and there is unpublished evidence of still other Kell antigens not produced by this Kell amorph, which is presently known as Ko. The amorph that produces none of the Rh factors is known as --.--. Any of the types in category 4 may eventually be shown to be genetic deletions, inversions, or translocations. Or, possibly, other antigenic alternatives, such as H in the ABO system, may turn up. None of these types appears to be caused by independent modifier genes, on the basis of family studies that have been reported. The high frequency of type Fy (a-b-) in Negroes (the one known exception to the general rarity of "minus minus" types), suggests that this may be different from the others of category 4, Table 1. It may, for example, more closely resemble the common type O.
In any or all of the known “minus minus” types, there may be present still another antigen of the same blood-group family, which is so universal that it cannot be detected as a blood-group factor. Conceivably, such universal antigens might be detectable by dosage titrations of serum or red cell eluates from persons with idiopathic acquired hemolytic anemia. I have no idea how much work may have been done along this line; such investigations would be based on the assumption that auto-antibodies might be formed that would detect such antigens, just as other auto-antibodies have detected the antigen e and others, and also that the “minus minus” phenotype might have an excess of the universal antigen. It seems unlikely that many, if any, of the presently-known “minus minus” types are homozygous for a gene that produces an uncommon antigen; most of the large number of rare antigens have been quite thoroughly investigated in exploration of this possibility. In not a single case* has an uncommon antigen been found to fill the gap caused by absence of two alternative antigens, a quite astonishing fact considering the large numbers involved.

Most of the “minus minus” phenotypes are very rare. This is consistent with the idea that the “amorphs” are simply genes lost by deletion. Presumably deletions, even small ones, would be disadvantageous in terms of genetic “fitness,” which would keep the frequency of such chromosomes very low. The very high incidence of consanguinity in known examples of “minus minus” phenotype in the Kell and Rh systems (Race and Sanger14) is an interesting and unexplained facet of the problem.

References


* Except for the debatable case of Cw in the phenotype C-c-Cw+D+E-e-.