An Analysis of the ABO Blood Group Clines in Europe

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ABSTRACT With estimates of the fitnesses of the genotypes and selection by incompatibility for the ABO locus which seem reasonable given the state of knowledge, a computer model has been developed to replicate the clines of the A and B genes in Europe. With a fitness change in the BB and BO genotypes of as little as 0.5%, the differences in the frequencies in East and West Europe can be maintained at equilibrium. Appreciable changes in the amount of migration does not affect the equilibrium frequencies in the two areas significantly, while with no selection through incompatibility the equilibrium frequencies were changed about 5%.

For many years the east-west cline in the frequency of the blood group B gene in Europe has been known. The increase in the B gene frequency in Eastern Europe has generally been attributed to an Asiatic origin (Haldane, '40), while Candela ('42) was more specific in attributing it to the incursions of Mongoloid peoples into Europe from the fifth to the fifteenth centuries A. D. Recently, this explanation has been increasingly questioned (e.g., Coon, '65), and this doubt has been due primarily to the gradual recognition of the importance of natural selection as a force maintaining the frequencies of the ABO blood group genes. Brues ('54) showed that the world frequencies were clustered in one small area of the distribution, which implied that some force was maintaining them in this restricted range, and the great amount of work showing the presence of maternal-fetal incompatibility and of differential susceptibility to disease at the ABO locus have implicated selection as this force. However, so many of the investigations are contradictory that it is difficult to draw explicit conclusions from them (for reviews of the various aspects of the ABO blood groups, see Reed, '67; Hiraizumi, '64; Otten, '67; Cohen and Sayre, '68). The purpose of this paper is to attempt to replicate the clines for the ABO blood group genes in Europe by assigning fitnesses to the genotypes which seem reasonable estimates given the nature of our knowledge of the ABO blood groups and by estimating the pattern and amount of gene flow among European populations.

The east-west cline in the B blood group gene is illustrated on figures 1–3. The data are taken for the most part from Mourant et al. ('58), but the Spanish frequencies are from Guillen ('59), the French from Vallois and Marquer ('64), the Swedish from Beckman ('59), and the Finnish from Erikson et al. ('62). In Central Europe the abrupt rise in the B frequency occurs between the Germanic and Slavic peoples, although through Austria there seems to be a more gradual rise. On the other hand, through Scandinavia the rise is much more gradual. This may be due to the fact that in many parts of Sweden the population is almost 50% Finnish, which appears to be more gene flow than is found in Central Europe. In contrast to the east-west cline in the B frequency, figure 4 shows a north-south transect which shows little if any change in either the A or B gene frequencies. However, as is shown in figure 4, stature does decrease from north to south in Europe. The data on stature are from Chamla ('64) and Lundman ('50). On figure 3 the cline in stature through Scandinavia is shown, but in this case it seems to be concordant with the cline in blood group B. For Scandinavia the data on stature are from Lundman ('50) and Kivalo ('57).

In order to replicate the equilibrium frequencies of the blood group genes in

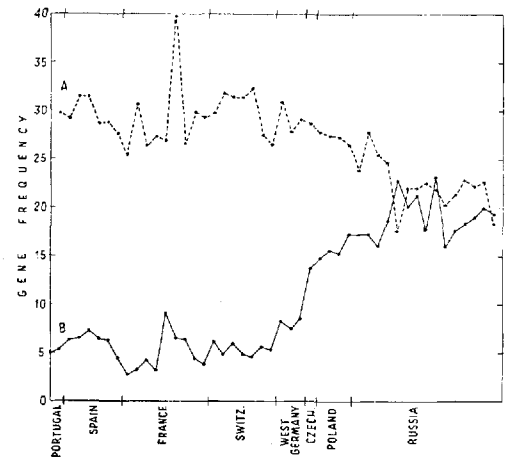

Fig. 1 The frequencies of the A(– – –) and the B(——) blood group genes on an approximately straight line from Lisbon to Molotov (Perm).

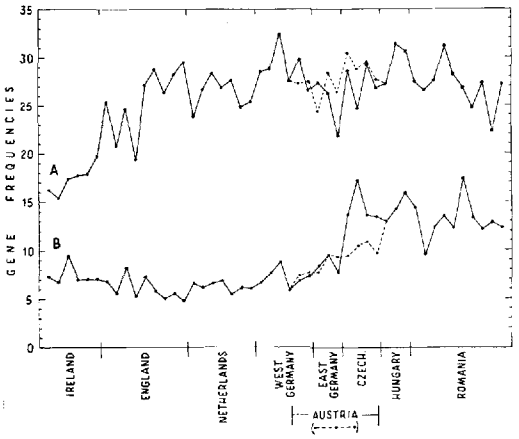

Fig. 2 The frequencies of the A and B genes on a line from County Mayo to Bucharest.

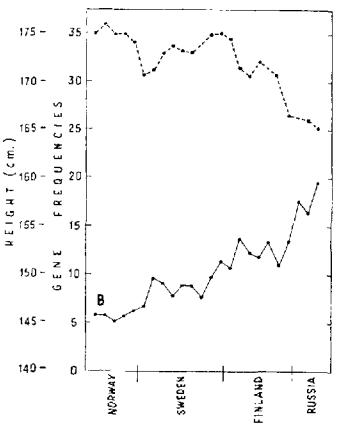

Fig. 3 The frequency of the blood group B gene (——) and average adult male stature (– – –) on a line from Western Norway to Archangel.

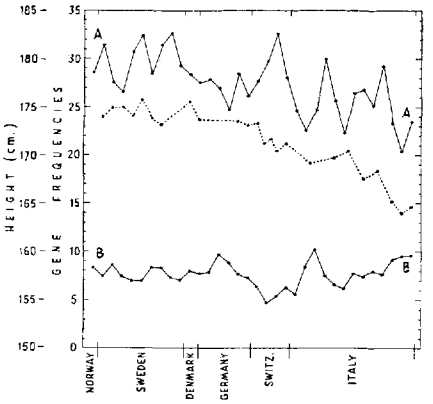

Fig. 4 The frequencies of the A and B blood group genes and average adult male stature (– – –) on a line from Northern Norway to Sicily.

Europe and thereby the clines, the fitnesses of the genotypes have to be estimated. For the general world frequencies, Brues ('63) estimated the genotype fitnesses to be: AA, 0.74, AB, 1.0, AO, 0.89, BB, 0.66, BO, 0.86 and OO, 0.79. Although these differences in fitness are difficult to detect since the AA cannot be distinguished from the AO genotype nor the BB from the BO genotype, the presence of a range in fitness of 33% for the ABO locus seems to be rather large. In addition, the equilibrium frequencies determined by these fitnesses and some incompatibility are not close to those found in the great majority of the world's populations. By segregation analysis Chung and Morton ('61) estimates the fitnesses to be: AA, 0.91, AB, 1.0, AO, 1.0, BB, 0.91, BO, 1.0 and OO, 0.92, with a reduction of 9% in the fitness of the AB, AO, and BO heterozygotes due to incompatibility. The equilibrium frequencies determined by this set of fitnesses are somewhat lower for the A and B genes than the world's average, but also to have gene frequency differences at equilibrium, the fitnesses of the A and B genotypes would have to be different. Of course, a cline does not have to be at equilibrium but could be the result of an advance of an advantageous gene through a

series of populations or of a marked change in the amount of gene flow among populations. In Europe the cline for the B gene may not be close to equilibrium because of the great changes in the populations of Europe in the last 200 years. In fact, Walter ('63) has found different B frequencies in the socio-economic classes in Westphalia and attributes the high B frequency in the workers to their eastern origins. However, we will assume the cline is stable or in other words the gene frequencies are close to equilibrium.

Since there are many more associations of diseases with blood group A, the fitness differences for the A genotypes would seem to have a wider range than the B genotypes. There is also no correlation — positive or negative — between the A and B frequencies in most areas of the world, so the common heterozygote would not appear to have a very low fitness as for the abnormal hemoglobins nor a very high fitness. In addition, the AB and OO genotypes do not seem to show marked changes in frequency with age, so they would seem to have comparable fitnesses. Thus, with a maximum range of 10% in fitness the genotype fitnesses have been estimated to be: AA, 0.90, AB, 0.95, AO, 1.0, BB, 0.925

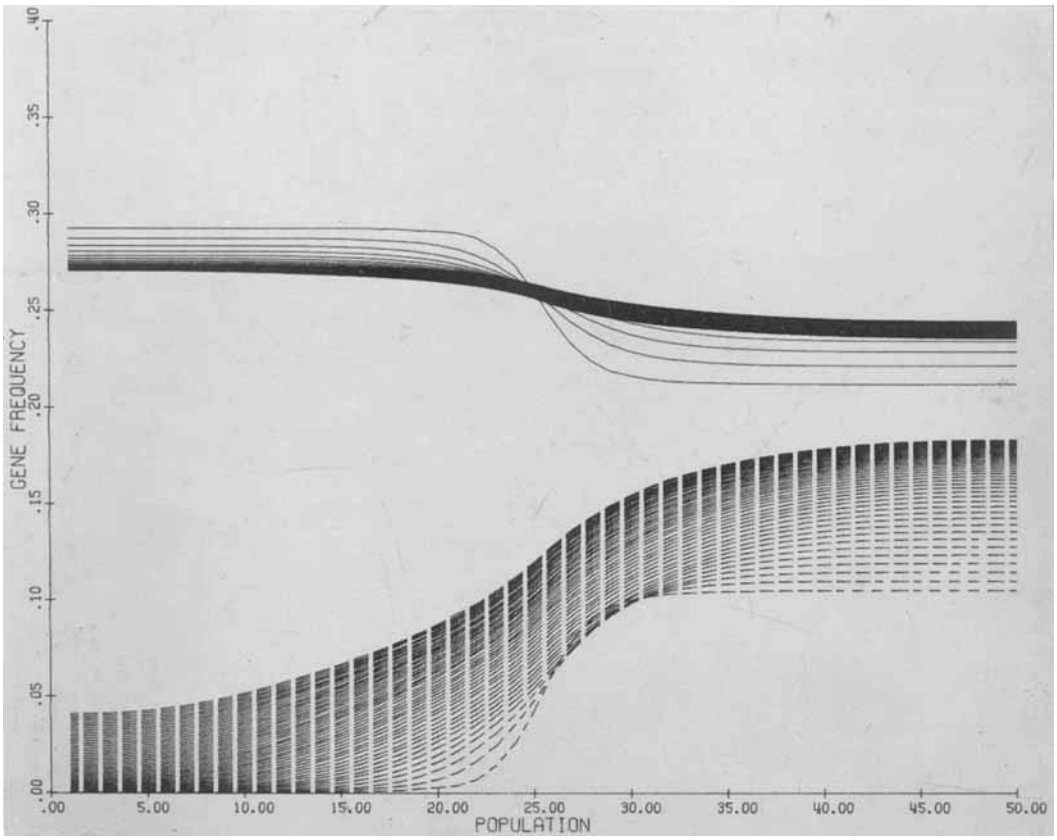

Fig. 5 The clines for the A(——) and B(– – –) genes along a sequence of 50 populations with fitnesses AA, 0.90, AB, 0.95, AO, 1.0, BB, 0.925, BO, 0.975, OO, 0.94 in the first 25 populations and with BB, 0.93 and BO, 0.98 in the last 25, with 15% migration which for the ith population is apportioned 40% to i ± 1, 9% to i ± 2, and 2% to a population randomly chosen from i ± 10. The cline is drawn every twentieth generation and the initial frequencies for populations 1 to 25, AA, 0.09, AB, 0.00, AO, 0.42, BB, 0.00, BO, 0.00, OO, 0.49; and for 26 through 50, AA, 0.04, AB, 0.04, AO, 0.28, BB, 0.01, BO, 0.14, OO, 0.49. IA = 0.10 and IB = 0.08 for all populations. (Note, the ith, ith ± 1, and ith ± 2 populations are included in the random selection.)

or 0.93, BO, 0.975 or 0.98 and OO, 0.94. The incompatibility of the A and B genes with OO mothers has been assumed to result in 10% and 8% selection, respectively, while the selection in other incompatible matings has been assumed to be O. The fertility studies have been equivocal with regard to this problem, but almost all clinical cases of incompatibility have occurred in OO mothers.

The marriage patterns and hence the amount of gene flow among most human isolates is principally a function of the distance between them (Sutter and Tran-Ngoc-Toan, '57; Cavalli-Sforza et al., '64; Boyce et al., '67). In the agrarian societies of Europe between 60 and 90% of the marriages were contracted within the same village or parish (Bunak, '67; Fraccaro, '58). As an approximation to this pattern, the model has apportioned 40% of the migration to the adjacent isolates, 9% to those adjacent to the adjacent ones, and 2% randomly distributed to one isolate of a larger group which, together with the total amount of migration, was allowed to vary. Thus, for the ith population the frequency of any one of the 6 genotypes at the ABO locus would be:

$$G(i) = (1-m)G'(i) + 0.4mG(i+1) + 0.4mG(i-1) + 0.09mG(i+2) + 0.09mG(i-2) + 0.02mG(r),$$

where m is the amount of migration, r some randomly determined population, and $G'(i)$ the frequency of the genotype in the next generation due to selection within the ith population.

With W the fitness of the appropriate genotype, IA and IB the selection due to

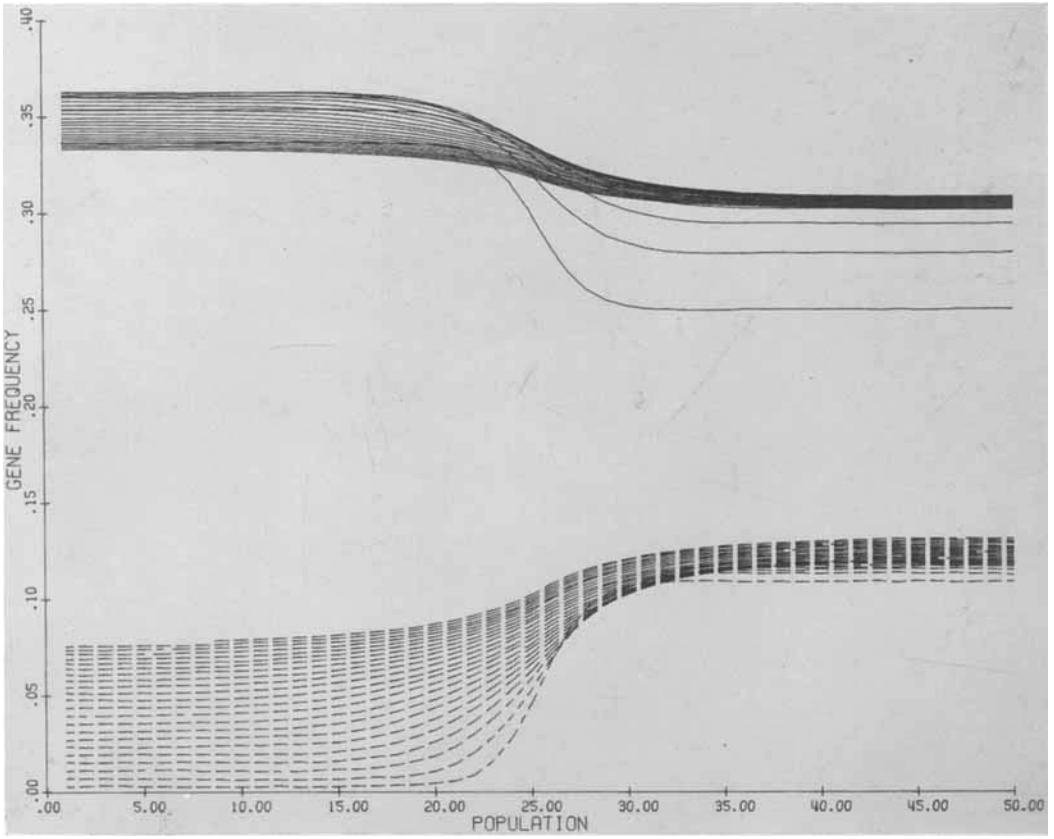

Fig. 6 The clines for the A(——) and B(– – –) genes with the same values as figure 5 except for IA and IB = O, and the 2% random migration can originate from any population along the cline.

incompatibility, and C the compensation which has been assumed to be O, the frequencies of the 6 genotypes in the next generation will be the following when they are divided by their sum in order to adjust the total of the 6 to 1.0:

$$AA' = W_{AA}[AA(AA + AB + AO) + 0.5AO(AB) + 0.25AO^2 + 0.25AB^2]$$

$$AB' = W_{AB}[AA(AB + BB + BO) + BB(AO + AB + AA) + 0.5AB^2 + 0.5AO(AB) + 0.5AB(BO) + 0.5AO(BO)]$$

$$AO' = W_{AO}[AA(AO + BO + OO) + 0.5AB(AO + BO + OO) + 0.5AO(AO + BO + OO) + (1 - IA)(AA(OO) + 0.5AB(OO) + 0.5AO(OO))]$$

$$BB' = W_{BB}[BB(AB + BB + BO) + 0.5AB(BO) + 0.25BO^2 + 0.25AB^2]$$

$$BO' = W_{BO}[BB(AO + BO + OO) + 0.5AB(AO + BO + OO) + 0.5BO(AO + BO + OO) + (1 - IB)(BB(OO) + 0.5AB(OO) + 0.5BO(OO))]$$

$$OO' = W_{OO}[OO(AO + BO + OO) + 0.25AO^2 + 0.25BO^2 + 0.5BO(AO) + 0.5C(OO)(AO + BO)]$$

By repeated substitution of the previous genotype values the new frequencies can be computed for the next generation for each population along the cline and then migration added as outlined in the last paragraph. In the following diagrams the resultant cline has been drawn every 20th generation.

With the fitnesses of the genotypes estimated above, figure 5 is a replication of the cline in the B blood group in Europe. Migration has been assumed to be 15%. Strictly speaking the total migration would usually be more than this for most human populations, but the gene flow along the cline is only of concern here; so that the isolates on opposite sides of any isolate would be approximately half of the isolates with which migration occurs. The B gene

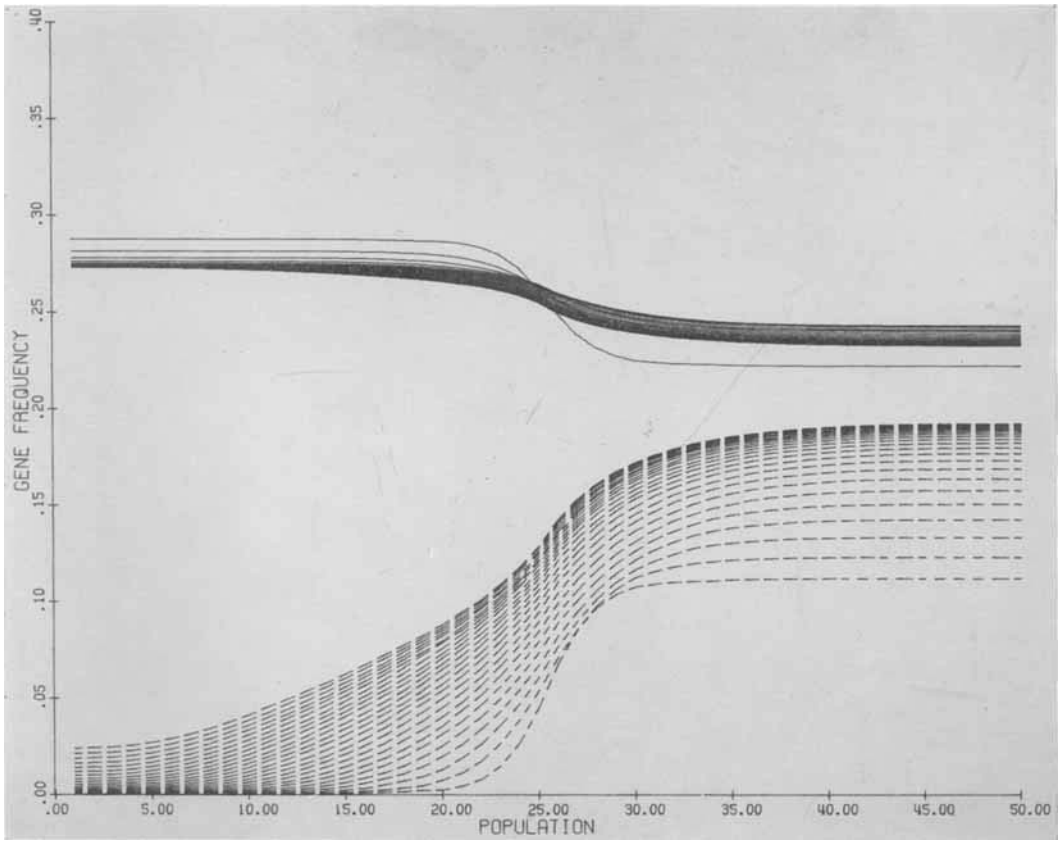

Fig. 7 The clines with the same values as figure 5 except that IA = 0.20, IB = 0.16, and AA, 0.80, AB, 0.90, AO, 1.0, BB, 0.85, BO, 0.95, and OO, 0.88 in populations 1 to 25, and BB, 0.86 and BO, 0.96 in populations 26 to 50.

has been started in appreciable frequencies in half of the populations, and it can be seen to increase toward the left. On the other hand the blood group A gene was begun with frequencies close to equlibrium, which it approaches quite rapidly. The broad dark band is indicative of the fact that the A frequency is close to equilibrium. The B gene, however, approaches equilibrium more slowly, and in this case with random gene flow assigned to some population within 10 populations on either side of the isolate in question the advance of the B gene is very slow. In fact the cline does not maintain a constant shape but flattens out. Even after 1000 generations or perhaps 25,000 years the B gene is still not up to equilibrium for most of the populations on the left of the graph. Although the time is much greater than that postulated by Candela ('42), the cline does not maintain a constant shape or wave front with this much selection and gene flow, so that gene flow could result in the very

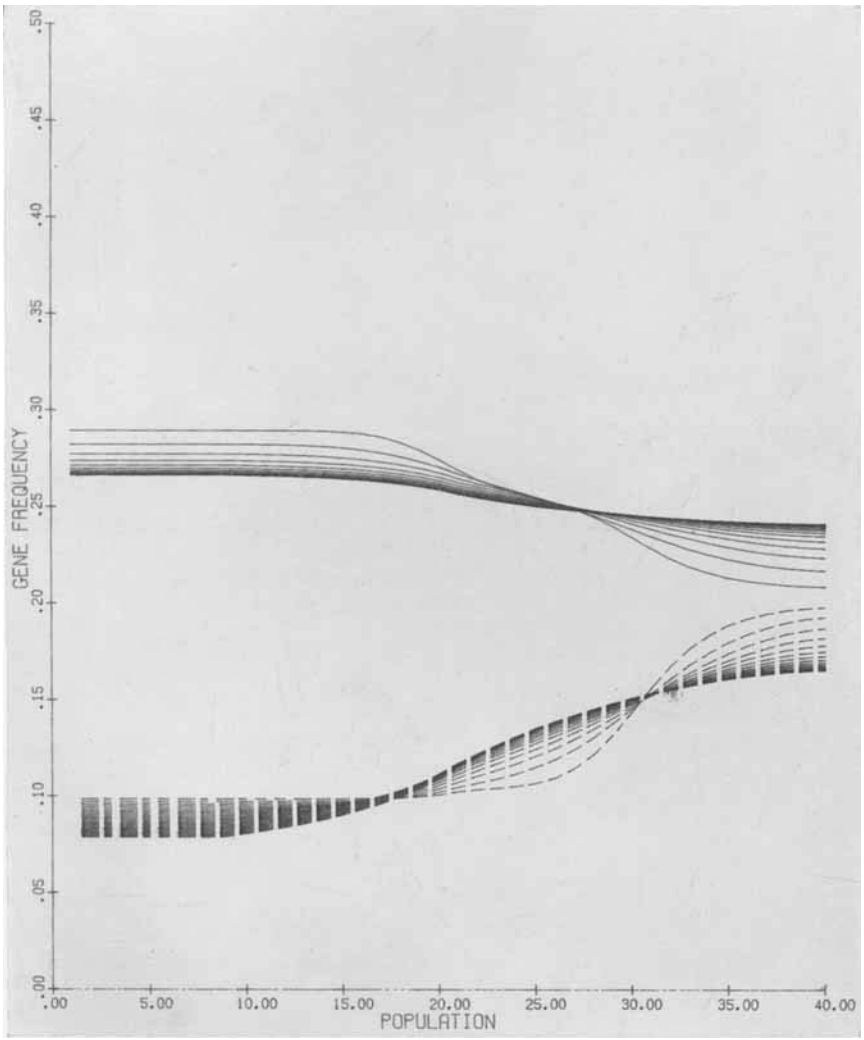

Fig. 8 The clines for the A and B genes with the same values for populations 1 to 20 and 21 to 40 as on figure 5 for populations 1 to 25 and 26 to 50, respectively, and 25% migration.

flat long cline in the B gene in Western Europe. One half of the populations have been assigned lower fitness values for the BB and BO genotypes, and these seem to result in a lower equilibrium frequency for the B gene which seems comparable to that in Western Europe. But this difference in fitnesses is astonishingly small — only 0.5%.

In order to determine the effect of incompatibility the same fitness values and initial gene frequencies were run with no selection due to incompatibility. Figure 6 shows the results, which indicate that up to 10% incompatibility selection has little effect on the equilibrium frequencies. However, this has resulted in an increase of 5% in the A gene frequency and a decrease in about 5% in the B gene frequency at equilibrium. In the 500 generations the program was run the frequencies did not get extremely close to equilibrium but were still approaching it, as can be seen from the absence of any dark band. For

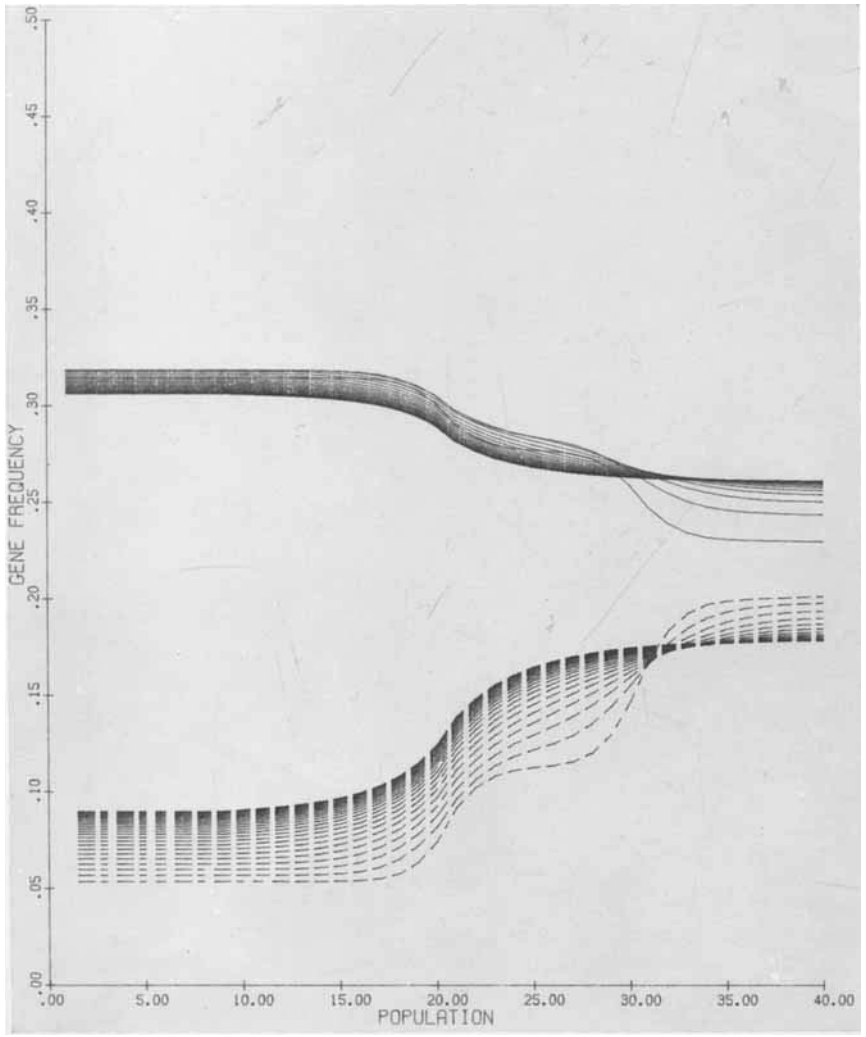

Fig. 9 The clines for the A and B genes with the same fitness values for the two halves of the series of populations as on figure 7 but with IA = 0.10 and IB = 0.08 and 10% migration.

this run the random gene flow was taken from any of the populations along the cline. This has increased the rate of advance of the B gene, and it has also appeared to have caused almost the complete absence of any cline. That this little gene flow could counterbalance the selection seems unexpected.

The same conditions were also run with selection against the zygotes and by incompatibility double that of figure 5. As is shown on figure 7, the cline is somewhat steeper and the rate of advance of the B gene almost double that shown on figure 5. The program was only run for one half the number of generations as figure 5 but the B gene has advanced as much. Finally, with the same fitnesses and incompatibilities, the gene flow was increased to 25% and the initial gene frequencies changed. The results are shown on figure 8. The cline is somewhat more gradual and like that found through Scandinavia. If the gene flow is reduced to 10% and the selection doubled, then the cline is shown on figure 9. It seems to approach that through Central Europe. Of course, these clines with only 40 or 50 populations are not directly comparable to the clines through Europe which include several hundreds of populations. Although the gene frequencies shown on the European clines are averages for several populations, the many assumptions necessary to construct the model make it uncertain whether the steepness of the replication of the model is an approximation of the actual cline. In any case, further data on the steep part of the cline in Central Europe which pertain to actual isolates will be necessary to settle the question, and the investigation of other more restricted clines of the ABO locus will help to determine the range in fitness values and the factors contributing to fitness at this locus. Although, as a beginning, the model has assumed fitness to be constant in each population, the fact that many epidemic diseases seem to be implicated as selective factors at the ABO locus probably means that fitness varies considerably from generation to generation.

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