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Analytic Review:

Some Current Problems of Human Population Genetics

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In recent years there has been a considerable increase of interest in human population genetics. Various motives have inspired this trend: (1) There can be no genetic analysis of human genetic data without an understanding of the principles of population genetics. The mathematics involved may be tedious but have largely been made negotiable, thanks to the increasing popularity of computers. (2) Human data may supply insight into some general evolutionary problems which are not so easily solved in other organisms; the wealth of material already accumulated or potentially available is enormous. (3) Physical anthropologists realize increasingly that this branch of genetics is the theoretical backbone for their work. Social and cultural anthropologists may soon start realizing that there are important areas of overlap. (4) Anything human tends to attract more curiosity and, at times of dwindling financial support for research, has perhaps a higher chance of being funded.

The usefulness of computers could not be overemphasized. Statistical methods that were available but not employed because of the heavy arithmetic involved are now usable in practice. Computers can also supply theoretical answers by Montecarlo or simulation methods to problems which are out of reach for mathematical techniques. Both advantages should be viewed with caution. Realism shows that in many biological estimations even the first significant digit may be in doubt. For this reason, the use of highly sophisticated methods requiring computers may sometimes generate perplexity, but by now it is often most economical to use programs already available for electronic computers. As to the use of computer simulation, it does not seem to be (usually at least) that exercise in "solipsism" which Morton denounces. It is true that in several cases an analytic technique can be found which answers the problem. But this may not be achievable before simulation; the heuristic value of simulating a complex phenomenon, in sorting out essential variables—or discovering unexpected conclusions—should not be minimized. Moreover, many of the mathematical theories of evolutionary genetics are themselves approximate or highly oversimplified, and computer simulation helps in showing their range of applicability.

It may be argued that the first motive is likely to decrease in importance with

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the advent of somatic cell genetics, which promises to transform the study of human inheritance into an experimental science. This development will certainly do away in part with the necessity of tracing those individuals or matings which furnish the only information for some problems but usually occur infrequently. Naturally, it will take some time before somatic cell genetics can tell us about dermatoglyphics, the shape of the nose, or a disease which, like the great majority of genetic diseases, has an unknown biochemical or even physiological basis. In fact, the necessity of population genetics will not be entirely destroyed, but, on the contrary, may be potentiated by somatic cell methods.

Other motives would in any case remain, and it can be assumed that the subject is likely to be popular for some time. This is, of course, fortunate as an actively growing field promises to be more intellectually rewarding than a stagnating one.

POLYMORPHISMS

I will not attempt a review, but simply point out some of the excitements and disillusionments which have characterized the more recent years. Perhaps the most stimulating event has been the experimental demonstration, announced almost at the same time on the basis of data from man [1] and Drosophila [2], that polymorphisms are much more common than might have been anticipated. At the latest count, 21 of 70 loci are polymorphic (in the English population) as tested by electrophoretic techniques [3]. Amino acid substitutions that do not involve a change of electric charge (and are therefore not detectable by these techniques) may bring the count to three times as many, but other unknowns may bias the factor of underestimation. It seems likely that almost every locus is polymorphic; however, evidence has been given that some categories of enzymes may be less polymorphic than others [4].

One important consequence of this finding for human genetics in general is that it should be possible to fill in relatively rapidly the map of human chromosomes. In Renwick's recent review [5], there are 11 autosomal linkage groups plus single genes assigned to chromosomes. The genes involved include several nonpolymorphic traits. Known polymorphisms may, in a few years, number 100. *Drosophila melanogaster* has been such a useful genetic organism because it has, among other things, over 1,000 markers known. An organism like man in which experimental work is not possible may require many more. With an average of 15% heterozygosity (limiting this computation to those loci that are polymorphic), the number of markers should be about seven times larger than that for an experimental organism in order to have a comparable chance of finding a desirable marker in the vicinity of an interesting region. Linkage could then be used as a tool in genetic analysis and for prediction of risks in counseling. Because man has more genes and more centimorgans than Drosophila, more markers may be needed to reach the same amount of relative genetic knowledge. It is difficult to guess how many decades will be necessary to reach this goal. But it would seem that the increase of knowledge on polymorphic markers is a very desirable aim that should be vigorously pursued. Moreover, somatic cell genetics gives good chances of mapping

those loci for which no variants have yet been detected in the human species. The only requirement is that their protein products show electrophoretic differences with their counterparts in another species with which human cell lines can be crossed. In other words, it allows use of polymorphisms "at large" (between different species). Finally, somatic cell genetics allows the use of loose linkage, since with hybrids whole chromosomes tend to segregate as units.

One cannot overemphasize the importance of increasing our knowledge of human polymorphisms. Many theoretical conclusions emerge from an analysis of polymorphic genes in populations; thus most of the work depends on them. One practical problem of increasing magnitude is that of keeping up with the mounting volume of data. The new edition of Mourant's celebrated book [6] is unfortunately still only in the offing. In addition, rare genetic diseases show frequency variation among ethnic groups [7, 8]. Part of this is likely to be the consequence of drift; if not, it may be traced to ecological differences, dietetic habits, etc. Our present knowledge is insufficient to determine if, for instance, Tay-Sachs disease has a high frequency among some Jewish groups because of drift or perhaps other reasons. Computations [9, 10] taking into account only the (unknown) number of founders seem insufficient to answer the problem, which should be considered in a more general setting.

Computers offer unprecedented opportunities for storage and retrieval of this type of information. A "genetic data bank" for genotype and gene frequencies for known markers in populations that have been investigated, and possibly for rare genetic diseases and their frequencies in various populations, seems an important initiative to be taken and to be made available on a service basis.

MUTATION AND SELECTION

The issue "panselectionism versus panneutralism" could be resolved, in principle, by having good estimates of a suitable sample of mutation rates and of the frequency distribution of selection coefficients of independent mutants [11]. But accurate measurement of mutation and of selection rates has proved difficult in man, particularly because of the enormous amount of work involved. Those mutation rates in man that have been adequately estimated are a highly select little group: they are all dominant or sex-linked deleterious, *frequent* mutations. For almost all it is not known if they involve one or more loci; the latter alternative is more likely. Trials to avoid the various biases due to the choice of more frequent mutations can only indicate that the average mutation rate is smaller—probably much smaller—than formerly believed. One ascertainment bias which had not formerly been taken into account is the mere fact that a rare mutation is less likely to be included in a sample of mutation rates because of its rarity. The greater the variation in mutation rates, the stronger the effect [12, pp. 104–110, 115–117]. This has been criticized [13] on two grounds. (1) The evidence from Hiroshima and Nagasaki "suggests that the doubling dose for mutation of acute radiation is probably at least 30 rads"; and it would have to be less if mutation rates were

lower than usually believed. But the information on the doubling dose from Hiroshima and Nagasaki is extremely limited [14]. (2) We have made the assumption "that the proportion of mutants giving rise to a recognized phenotype is rather homogeneous among loci." Morton's argument, which should be examined in detail in his presentation [13], first considers and then later on ignores the fact that we are limiting our consideration to deleterious mutations. Even apart from this essential aspect, one should take with caution his a priori statement that "the law of large numbers should guarantee a rather homogeneous mutation rate per cistron" until experimental data show better agreement with this expectation.

The best way adequately to estimate average mutation rates (detrimental or not) would be to use a suitable sample of sufficiently well-known proteins. The number of individuals to be analyzed is likely to be very large and would make the enterprise a very ambitious one. The issue of mutation rates is becoming of greater and greater importance with the mounting level of pollution and the potential mutagenic activity of some of the polluting products. This should provide adequate stimulus [14].

Similar considerations apply to the measurement of natural selection. For deleterious mutations, selective disadvantages are relatively easy to measure and the techniques developed, as well as the knowledge accumulated for public health reasons, should make the estimate of fitnesses especially easy and accurate. So far, this has happened only to a limited extent. A discussion of the little-known (but necessary) demographic methods, inspired by the pioneering analysis R. A. Fisher made in 1930 and reported in *The Genetical Theory of Natural Selection,* can be found in [12, chap. 6].

Deleterious mutations are easier to analyze because they involve higher, and therefore more easily measurable, selective disadvantages. But those advantages and disadvantages that are small are very difficult to measure accurately. The size of the sample necessary increases inversely with the square of the selection coefficient. Data on hemoglobin (Hb) S bear on tens of thousands of individuals in areas sufficiently restricted to be considered fairly homogeneous environmentally. They are sufficient to estimate with a reasonable standard error a selective advantage of almost 10% for Hb S heterozygotes over Hb A homozygotes in the presence of heavy malarial infestation. Small selective advantages or disadvantages in heterozygotes for recessive diseases may have substantial effects in determining equilibria but would require hundreds of thousands or millions of individuals for an adequate estimate.

One genetic adaptation that is emerging from recent work is lactose tolerance in adults [15]. It is probably genetic [16]. This trait seems to be common or extremely common only in populations which have established the custom of having milk regularly in their diet after weaning. It is rare or absent in others. The trait may have begun increasing with the spread of domestication of cattle; this gives at most some 10,000 years for the genetic adaptation to have taken place. The selection coefficient attached to the trait should be, from these historical considerations

and present figures in the population, of the order 2%–3%. A direct estimate would require the impossible task (today, at least) of testing an enormous number of individuals.

In other cases, demographic and public health data may allow us to estimate fairly small selection coefficients; thus, that attached to the O phenotype in ABO blood groups because of predisposition to ulcer is of the order 1/10,000 or less [12, p. 303]. Naturally, this is only one facet, and probably a minor one, of selection in ABO blood groups. It is very unfortunate that this system, so widely studied for the well-known clinical reasons, has not been amenable to a simple means of distinguishing A and B homozygotes from their respective heterozygotes. The confounding that results has probably considerably impeded the understanding of natural selection in the system. The lingering suspicion of heterozygote advantage could otherwise well have had a clearer, more fruitful demonstration. The importance of heterozygote advantage, or genetic homeostasis in general, remains one of those facts which almost everybody believes but whose relative role is difficult to assess in a quantitative way. The gradual realization that, rather than considering genes separately each should be viewed as part of the chromosome region to which it belongs, is likely to be an increasingly important avenue of thought [17]. The possibility that HL-A may borrow its homeostatic mechanism from neighboring genes for the immune response [18] is an important, if still hypothetical, example.

The measurement of natural selection and of some mutation rates in man will undoubtedly develop in a much more satisfactory, reasonable, and economic way when methods of record linking of available data (demographic, medical, etc.) have made further progress. The pioneering work of Newcombe has shown the potentials of the method. Present limits are still numerous—among them, the accuracy and fidelity of data from different hospitals and health services and the difficulty connected with possible breach of privacy. Perhaps this approach must wait for a better world where, among other things, secrecy is not necessary for protection of the individual; this is likely to require some wait.

DRIFT AND POPULATION STRUCTURE

Drift versus Selection: Drift Wins

Chance, in the form of "random genetic drift," has certainly been one of the winners in the evolutionary work of recent years. For a long time its role has been obscure to all but its first great theoretician, S. Wright. Analysis of the role of drift demands good knowledge of demographic quantities that affect it, such as population sizes, age distributions, age-specific death rates and birthrates, distributions of progeny size, and migration patterns. Man is, in this respect, an organism of choice. Unfortunately, this demographic information is required over some generations, or at least one needs a guarantee that no great changes have taken place. This limits the chances of accurate study to a relatively small number of populations. In principle, however, given the knowledge of the quantities listed, the varia-

tion of gene frequencies between subgroups of a population can be predicted and compared with one actually observed.

Under these conditions, the problem of selection versus drift can be put in clear-cut terms. As selection itself is protean and not always reducible to a simple hypothesis to be tested, it seems preferable to formulate the problem as follows: what variation would be expected if drift alone (but not selection) operates? It should be clearly understood that when speaking of "drift alone," the effects of migration and the other demographic factors are included. This formulation, of course, leaves open the possibility of small, undetectable amounts of selection being operative, and the power of the test is a function of the number of individuals tested. The number tested increases with the size of the area considered, but then the heterogeneity of environmental differences and, therefore, of locally different selective conditions (and other sources of heterogeneity) increases. These inherent limitations may have to be kept in mind.

A program of simulation set up to predict the heterogeneity expected in a real population of the Parma Valley [19] showed that the prediction by a simpler analytic approach, called "the migration matrix," was sufficient for most purposes, giving a correct estimate of the amount of variation between villages due to drift [12, pp. 449 ff.; 20, 21]. The migration matrix indicates the migration rate from village i to village j. This should be available for all pairs of villages in the area considered, the rate being computed from the number of children born in village j whose parents were born in village i. In addition, the migration rates into each village from outside the area investigated should be known. Imaizumi et al. [22] have criticized our analytic method on the grounds that for certain values of N (population size) and migration rates—which happen to be outside the range of interest for humans—the numerical approximation is poor. But the method they have proposed in its place, based on Malécot's early suggestion [23], fails to appreciate one important aspect of the problem. Malécot's method was designed to test the importance of mutation (or of stabilizing selection) and thus imposed a constant "recall coefficient" incorporating all stabilizing forces (mutation, stabilizing selection, etc.). Mutation rates are known to be negligible in this context and the early hopes of estimating stabilizing selection in this way [24] have vanished [13, 25] with the realization that the recall coefficient that can be estimated really depends on migration from outside the area studied. This is really different for every village, but the method given in [22] fails to take this into account. It merely computes an average coefficient of stabilization, equal for every village, which is unrealistic since migration from the outside is likely to be different for every village. Actually the situation is even more complex [26] because migration from the outside can come from various sources; if these are heterogeneous the expected variation will be higher. In a paper in this issue, Wagener [27] extends our method to cover this aspect of the problem and shows that the increase in variation due to this refinement is not large. She reaches this conclusion using Ward and Neel's data on the Makiritare [26] as a numerical illustration. She acknowledges that for various reasons the results of the application to the

Makiritare cannot be considered as final. For example, some corrections to the computed "observed" variation of the Makiritare still have to be made for which published data are not sufficient. Two other reasons are sampling bias and the fact that the population was sampled almost completely, creating a "redundancy" whereby many genes were counted two or more times in the various relatives sampled. It is likely that when all corrections are applied, the agreement between the observed and expected variation in the Makiritare will improve considerably. But already at this stage, there is no significant difference.

A recent survey of applications of the migration matrix method [21] shows that the "microgeographic" variation encountered in the cases so far studied is at least approximately accounted for by drift alone. Unfortunately, these estimates can hardly be accurate, for all methods so far devised of measuring drift effects involve, directly or indirectly, the computation of squares or products of gene frequencies. This is true whether variances, genetic distances, kinships, homozygosity coefficients, etc., are computed. Squares or products of gene frequencies have unfortunate statistical properties which confer to them high standard errors, so that estimates are rough. An increase in the number of studies may help in part to overcome this difficulty. It should be noted that all populations studied so far have low densities and/or low migrations, making the relative importance of drift a priori more likely.

Selection

The fact that drift comes out a winner over selection in these studies of microgeographic variation should not obscure the issue of selection versus drift in "molecular" evolution, where the evolutionary game is played essentially at the level of the whole species and thus much larger population sizes are involved. This relatively reduces the role of drift, but does not destroy it entirely.

When whole ethnic groups of the same species are compared, we are considering large populations and a sample of environments as heterogeneous as the whole world can offer. It would not be surprising to find selection at work—and one does. One criterion that drift alone is operating is that all alleles should show the same variation in gene frequencies between subgroups when the variation is appropriately measured. This appropriate measure is a "Wahlund" variance or simply f (the variance of gene frequency of a given allele between populations, σ^2, divided by $\overline{p}\ (1 - \overline{p})$, where $\overline{p}$ is the mean gene frequency). The application of this criterion in the analysis of microgeographic variation, when the environment can only vary modestly, gave (so far) a verdict of "drift alone." When applied to the variation among ethnic groups, the results are different ([28, 29]; table 1).

They prove that selection, not only drift, is at work because drift alone would make this variation homogeneous for all alleles. Selection could operate here in various ways. It could increase f, the estimate of variation between ethnic groups, at the loci that show more variation by being different in different environments

TABLE 1

VARIATION OF SOME GENE FREQUENCIES AMONG ETHNIC GROUPS, WHICH APPROXIMATELY REPRESENT THE WORLD POPULATION

Variation	Alleles or Loci
Small ($f < .05$)	Kell, most HL-A alleles
Intermediate ($.05 < f < .15$)	ABO, MN, Hb S
High ($.15 < f < .5$)	Rh_0 and some other Rh alleles; Fy
Very High ($.5 < f < 1$)	Adult lactose intolerance; most Gm haplotypes

NOTE.—The measure of variation, f, is described in the text.

(differential selection); it could have the same effect by changing at random over both time and space, as in "selective drift" [30].

However, selection could also have the opposite effect, of stabilizing gene frequencies by homeostasis (selection in favor of heterozygotes, or at closely linked heterotic loci); this would lower f.

If we knew enough about the demography of the process that led to ethnic differentiation, we could predict one f value or range of values giving the variation between ethnic groups expected because of drift; this would set a useful standard for comparison. We do not yet have this knowledge. However, we know, for instance, that lactose tolerance in adults has been subject to widely different selective conditions due to dietetic habits, thus reaching almost 100% frequency among northern Europeans and remaining close to 0% in others [15]. We are therefore not surprised to find it in the category showing the highest variation. It is also likely that other extremely variable genes, such as many haplotypes of the Gm system, are subject to differential selection or selective drift. For Gm, the immediate suggestion is that variation of the gamma globulin molecule affects its specific antibody activities, at least in part. Hints that this may be true are available: the response to flagellin, an antigen from *Salmonella adelaide,* was associated with Gm groups [31]; differences in Rh incompatibility according to Gm groups are also reported [32]. Since infectious diseases are likely to cause the greatest fluctuations over time and space of selective conditions, the high ethnic variation of Gm genes, especially when haplotypes rather than antigens are considered [33], is not unexpected and may very well be a response to variable selection.

At the opposite extreme of the range of variation among ethnic groups is HL-A; the early suspicion of this by Bodmer and Bodmer [34] has been confirmed by the large amount of material now accumulated. If there is homeostasis at HL-A due to linkage with immune response [18], then the mechanisms of natural selection at the latter genes must be of a substantially different nature from that in Gm, which shows no homeostasis (by the criterion of ethnic variation). Still, both Gm and immune response may be involved in mechanisms of immune defense.

It can therefore be said that selection is responsible, though by different mech-

anisms, both for high f values (variable or differential selection) and for low f values (homeostasis). It is worth adding that intermediate f values are not necessarily due to drift alone. An example is Hb S, which is affected both by homeostatic selection (when malaria is present) and by variable selection (since malaria is present only in some environments). The two mechanisms balance each other and give to this allele an intermediate position on the f scale.

GENETIC DISTANCE

Studies of population structure have witnessed a considerable flourishing of methods for measuring genetic distance (see, for example, [35]). The high correlation among them makes the choice somewhat trivial when purposes involve internal comparisons only. Those methods which do not require avoidable matrix inversion are, as a minimum, simpler. The choice is not so trivial if distance measurements are required that are proportional to evolutionary time, as in phylogenetic analysis (see below). This demands the hypothesizing of the evolutionary causes of divergence (drift, selection, and which type of selection) and are subject, inevitably, to the validity of such hypotheses.

I am somewhat worried by the use of the words "kinship" and "distance" almost interchangeably, even keeping in mind that a kinship is usually a similarity coefficient, not a dissimilarity coefficient as distance is. I am perhaps in part responsible for the custom. The time may be ripe for a sharper distinction. A kinship (like an inbreeding coefficient, to which it is very closely tied) is a measurement of identity of genes *by descent*.* A distance is a measurement of genetic differences of genes *by nature*. Two individuals or populations may have a very high kinship and be genetically different if different selection forces acted on them. The reverse may be true. Methods of investigation of identity of genes by nature (the study of gene frequencies) differ radically from those of identity by descent (the study of pedigrees).

It seems to me that the best idea is to reserve the words "genetic distance" for measurements that depend on differences in gene frequencies (or functions of them). The scale used may be important, especially for phylogenetic considerations, as we shall see. Thus, a "Wahlund variance" f as used in table 1, if referred to two populations is a (squared) genetic distance between them, for it can be written in terms of (squares of) differences of gene frequencies. Under some conditions it can be equated to F_{ST}, an inbreeding coefficient defined by S. Wright (that of a subpopulation to the total).† This and other considerations lead to

* "Kinship" was introduced by Malécot [36]. It refers to two individuals, I and L, and is the probability that a gene taken at random from the two at one locus of I is identical by descent with a gene taken at random from L at the same locus. The inbreeding coefficient of an individual is identical with the kinship of his parents. In the English translation of the original work by Malécot (first published in 1948), the "coefficient de parenté" was translated "coefficient of coancestry," but the term "kinship" is in customary use.

† One element of confusion is that some kinship (and inbreeding coefficients) measure similarity, others dissimilarity. In the study of isolation by distance, for example, a measurement of kinship between two populations A and B is the average coefficient of kinship between

formulas that may transform distances into kinships (and inbreeding coefficients) or vice versa, under assumptions that are usually not specified.

The question remains that gene frequencies are based on the *nature,* not the descent, of genes. Kinship is based on the latter, and kinship should be measured from data on descent, that is, pedigrees. It would thus seem that it is best to reserve the word "kinship" (and its closely allied "inbreeding") to measurements based on pedigrees. The possibility of "bioassaying" kinship from gene frequencies has been championed by Morton et al. [37]. Some of the perplexities raised by this approach have been expressed in a recent review [38].

SYNTHETIC DESCRIPTIONS OF POPULATIONS

Population data are bulky so that synthetic descriptions are welcome. A useful, but perhaps even too synthetic, description is obtained by a method that usually goes by the name of "isolation by distance." To this purpose, theoretical models are used [36, 39–41] in which the total population is either subdivided into subpopulations all of equal size, all exchanging equally with neighbors (stepping-stone models), or the population is geographically distributed continuously and migrates homogeneously. The two theoretical models give similar, in some cases superimposable, results. They are somewhat rigid and their adaptation to reality is difficult. For some time the hope had been raised that they might serve the same purposes for which the migration matrix methods mentioned before were developed, namely, to assess the relative roles of drift and selection. However, many obstacles arose: the difficulties of fitting theoretically useful distributions to actual migration data and of distinguishing long-range and short-range migration; the necessity of using large areas of territory for this approach but still pinpointing the origin of each individual; the inevitable ecological, social, and historical heterogeneities of large areas to which this approach should preferably be applied; the assumption of equilibrium in the absence of knowledge of the time necessary to reach it—which may be long; the weakness of the theory in critical aspects as at zero distance, or as a function of dimensions; the inconsistency of results obtained with different approaches, like pedigrees and genetic markers. All these factors leave reasonable doubt, at the moment, about the possibility of raising this approach from a strictly descriptive level to that of measuring meaningful quantities whose validity can be tested by independent methods of measurement. In the best cases, straight lines are obtained between the logarithm of kinship and geographic distance (see [42] for summary), but the parameters of the straight lines have remained essentially uninterpreted [13, pp. 114–115]. This representation may still serve some comparative purposes. Reduction of all the variation observed to just two parameters, when feasible and valid, is a useful achievement. But if no precise hypothesis is

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two individuals, one belonging to A and the other to B. This is a measure of similarity and decreases, on the average, with increasing geographic distance between A and B. On the other hand, an inbreeding coefficient (F_{ST}) relating subpopulations S to a total population T formed by pooling them was shown by S. Wright to be equal to the "Wahlund variance" f defined in the previous section. A variance is, of course, a measure of dissimilarity.

being tested, the result is meager. Moreover, the total sacrifice of all the information in order to reduce genetic information to a measurement, "kinship" [37] (with an unknown proportionality constant to the true kinship), does not seem justified. The description thus obtained is welcome for some purposes, but in general is somewhat bare.

Other methods have been suggested which offer richer description. A standard statistical method, principal components analysis and all its modifications, has the great descriptive advantage of giving "genetic maps" of populations in which any number of markers can be reduced to two or three dimensions, thus making them easily visualized by the human mind. The advantage of the method is that of reaching this graphical aim with as little sacrifice of the available information as possible. The amount sacrificed can also be estimated. When this approach was tried on a representative sample of human ethnic groups, the first two principal components were found to explain about 50% of the total variation and gave rise to a map reminiscent of the geographic map [43; 12, p. 712]. This may encourage the concept that geographic distance is an important variable, but also that it is not the only one. A more direct test of this and other interpretations of genetic maps could be done in many ways, but perhaps the most interesting one methodologically is offered by recent developments in "multidimensional scaling." The rotational test by Gower [44] may also allow useful comparisons of various types of distance measurements: genetic, geographic, linguistic, etc. It may be similar to (or perhaps identical with) the test used in figure 1 of Lalouel and Morton [45] to compare genetics and geography.

Still another way of condensing the information on many populations in a simple diagram is a recourse to trees or dendrograms. This is widely used in taxonomy, and recently much work has been done to make taxonomic methods quantitative. However, trees also have somewhat unique phylogenetic implications and a separate analysis will be given in what follows.

TREES AND PHYLOGENETIC ANALYSIS

The use of "trees" in biological systematics and evolution has had two distinct purposes. Their introduction, by Darwin, was clearly designed to convey the idea of phylogenetic origin. Trees describing evolutionary origin are often called (perhaps somewhat pompously) "cladograms." In the use of trees for purely descriptive purposes of similarity between species or other taxonomic units, that is, as pure hierarchical classifications ("dendrograms"), taxonomists have usually shied away from the obvious phylogenetic implications [46]. This was perhaps dictated by the prudent recognition that most phenotypic analyses are inadequate, especially if taken in isolation, to give an accurate representation of evolutionary origin. It would be difficult not to agree with them. Still, it is difficult to believe that when taxonomists justify their use of "dendrograms" for purposes that they describe only as "general," they really want to discard entirely evolutionary history. Probably what the word "general" really implies is the hope that the art of building dendrograms may, by further work, either be brought to sufficient preci-

sion to serve a really specified purpose, or that, with luck, the same dendrogram may serve all purposes. But it is well possible, of course, that different dendrograms may have to be used for the same group of organisms in order to satisfy the two purposes of classification and phylogenetic history.

In their paper in this issue, Lalouel and Morton [45] strongly emphasize that their use of dendrograms does not imply that they take them as cladograms. Their statement, "The assumption of a cladogram is only useful as an hypothesis to be tested against other evidence," is, of course, valid; in fact, one could replace the word "cladogram" with any other scientific hypothesis. Some people extrapolate this, thinking it to mean that one *cannot* build methods that are better than others for reconstructing phylogeny. Is it possible to obtain dendrograms that are more likely to be correct cladograms, joining in the use of this somewhat baroque terminology?

A little over 10 years ago, Anthony Edwards and I set ourselves this precise aim, which seemed to us a legitimate one. Since there are doubts of its legitimacy, it may be worth reviewing some postulates and some conclusions. The first consideration to which I would still strongly adhere is that genetic data are the best on which to build if we are interested in biological evolution. Lalouel and Morton [45] chose to discard a phylogenetic interpretation derived by Fitch and Neel from an analysis of genetic data because it did not agree with geographic, linguistic, and other evidence. In the particular case they may be right. But the desire to make conclusions derived from genetic data fully compatible with other knowledge from extremely different sources, say, geographic distance, should be tempered, for instance, by the knowledge that some tribes move more rapidly than their genes can change. This happens to be true at least for some of the tribes which Fitch and Neel [47] have analyzed. The lack of correlation with linguistic distances may seem more serious. However, we know that linguistic evolution, like any cultural one, is, on average, faster than the biological one. I may be unduly influenced by personal experience, but I cannot avoid citing one instance. In one group of Pygmies in the Ituri, who are (as far as one can say) genetically and sociologically fairly similar, three different linguistic groups exist: two of Bantu and one of Sudanic origin (none of them being presumably a "Pygmy" language). The legitimate desire to have all the evidence from various sources agreeing should not obscure the fact that for different traits (and, in general, under different conditions) different mechanisms of evolution operate.

At some stage, the problem becomes a semantic one. If one is interested in biological evolution, then it is genes that matter. It may sometimes be worth restating the obvious. American Indians are related biologically to Orientals even if they live at the extreme tip of South America (almost at the antipodes of northeastern Siberia) and probably have more biological similarity with northeastern Siberians, or even with Japanese or Chinese, than with the Argentinians or Chileans who live nearby but who are of European origin. Similarly, black Americans are biologically closer to Africans than to white Americans, even if they speak a dialect of English.

The main "postulate" in the game—valid for any type of evolution, not just the biological one—is that divergence between two groups tends to increase with the time since separation. (Quotation marks are added to indicate, as will be made clear later, that this may be expressed as a theorem rather than a postulate.) A corollary is that if quantitative use is to be made of this "postulate," measures of divergence must be adopted that are proportional to (or more generally a known function of) time elapsed. This requires either (1) the possibility of testing, at least in some favorable situations, that measures of divergence used are indeed proportional to time; or (2) that enough is known of the evolutionary mechanisms to predict which measures would satisfy this requirement. Ideally, one would like to be able to meet both requirements.

There are no very satisfactory data to test requirement 1 for human biological evolution, but a few rough possibilities exist, and it is hoped that knowledge will increase. As to requirement 2, the genetic theory of evolution shows that if drift only were responsible for evolution, with equal population sizes, then a simple function of Wahlund's variance f, $-\log(1-f)$, is proportional to time. If, on the other hand, differential selection (variable from place to place) is operating, then $\sqrt{f}$ is correct [48] and population size is unimportant. If selective drift is operating, another measure derived from the logit transformation of gene frequencies [49] is the correct one. With homeostatic selection probably the same situation applies as for drift.

It would seem that we cannot be so bold as to assume that we know, in each instance, which of the various cases applies. There are, however, criteria that can help us in making meaningful decisions; probably the best solution would be to use a different, suitable scale for each allele. A suitably chosen power of gene frequency functions may be the answer [49], since it encompasses all three of the scales suggested above.

An inquiry into the reasons behind the "postulate" of evolutionary divergence increasing with time shows that it is only when chance operates—be it because of true drift, selective drift, or in other ways—that we can place reasonable confidence in it. It is in a random walk that the squared distance increases proportionately to time. The distance between two particles starting at the same position that have been subject to Brownian motion satisfies this theorem, but only on the average; the actual distance has a wide probability distribution. If the particles move in many dimensions, which are the equivalent of many independent genes, the relative error of the estimate of mean distance decreases approximately with the inverse of the square root of the number of dimensions, that is, of independently evolving genes.

This is in sharp contrast with the statement by Lalouel and Morton [45] that "most of the distances measured . . . *reflect random evolution, making phylogenetic interpretation specious*" (my italics). A major danger in reconstructing phylogenetic history is just the opposite: that evolution is *not* random. Populations adapting separately to similar environments, for example, to the tropical forest, may undergo parallel evolution and all react in the same phenotypic way, say,

with small stature. Stature, introduced into our measure of divergence, will then indicate not so much phylogenetic history, but rather similarity of environments. I believe that if one could look at the genes determining stature instead of stature itself, one would probably still be able to see, in a number of cases, that a similar adaptation has been reached in genetically different ways when independent populations are considered. If this is true, analysis at the genotypic level gives a better chance of seeing the difference which is denied by the sole phenotypic analysis (in this particular case, the measurement of stature).

One extreme example of parallel evolution is adaptation to malaria. Even here, however, if many populations have responded by sickle cell anemia, others have done so by various types of thalassemia or different G6PD alleles. Probably if enough genes are considered or if the analysis is sufficiently refined, even cases of parallel evolution due to environmental similarity still satisfy the "postulate" and are thus susceptible to phylogenetic analysis. It is again randomness that can help us by determining which particular mutation occurred, which alleles were introduced by migration, or which genes of a polygenic system happened to react more than others to selection dictated by similar, but physically separated, environments.

One other major source of error in reconstructing evolution from genetic data is the problem of the constancy of evolutionary rates. This can be partially remedied by considering as many genes as possible. Even so, different environments, organisms, or populations may still have lower or higher rates of evolution overall. The effect of population size when only drift is operating is a simple but clear example of an effect on overall evolutionary rate. This consideration limits the validity of conclusions reached by methods that use constant evolutionary rates as basic assumptions. Maximum likelihood is one method that clearly uses this assumption. Recent work by Felsenstein [50] made this method applicable in practice, overcoming earlier limitations [51]. Another method which implicitly assumes constant evolutionary rates is "cluster analysis" (an extension of analysis of variance) [52]. Both methods generate what we have called "rooted" trees in which a single common ancestor (the "root") is clearly individualized.

Other methods (the model of "additive evolution" by least squares; and minimum path [53]) give "unrooted trees" where no remote ancestor is indicated. The former operates on the assumption that the amount of evolution is independent in the various branches, making distances in the various branches additive; the latter uses the somewhat dubious assumption of minimum evolution. When the constancy of evolutionary rates is unacceptable, reconstruction of rooted trees may not be possible and one may have to be content with unrooted trees. (Felsenstein's maximum likelihood method can also be operated to give unrooted trees.)

A simulation of a random evolutionary process with random fission has been analyzed with the various methods [54, 55]. As new methods become available it is hoped that they will be tested on this material. Few differences have been found among the various methods with the exception of minimum path, which is slightly inferior to the others when tested on this evolutionary model.

Incidentally, there have been gross exaggerations on the cost of such methods, which is really trivial when compared with that of assembling the data. With 15 populations the cost rarely exceeds $40.00 for any one method. This includes testing a reasonable sample of trees generated to improve the fit of an initial arbitrary tree, but not an exhaustive sample. The computer cost is largely determined by the number of trees tested, but an exhaustive analysis is to date prohibitive for more than seven populations. In an exhaustive analysis, the cost ($50.00 or less for seven populations) goes up to an extrapolated $600.00 adding just one extra population. The simulation experiments have shown that the probability of error is such that, with 15 populations, there are already on the average three errors in the tree when 20 independent characters are tested (total number of alleles minus number of loci). Thus, there is not much point in constructing trees of 15 populations or more unless many dozens, possibly hundreds, of independent characters are tested, which is rarely possible.

One further problem is that human populations are not fully isolated, as assumed in the simple evolutionary model of fission followed by independent evolution which was so far used in our simulations and which underlies some of the models used for analysis. The reconstruction will inevitably be severely affected. If the pattern of migration were a regular one, the problem would be soluble. But if there is a complex, irregular system of fusions following the fissions of the populations—as with Makiritare Indians—then the problem is difficult. Instead of a "tree" one may have to estimate a "network"; such methods do not yet exist. For fear of such complications, I have tried to restrict use of the methods of phylogenetic analyses to populations widely separated geographically and which have little, if any, exchange. I may have been wrong, for the analysis of the Makiritare data [26] showed a remarkable similarity between the "tree" obtained by consideration of 11 loci and the "network" shown by anthropological history. It may be that the methods of analysis, at least some of them, are more robust than might at first be believed. Or the true networks may be sufficiently uncomplicated that a tree representation is not a bad approximation.

Here is an interesting contrast. The same Makiritare data were analyzed by Lalouel and Morton [45] using a variety of methods. They conclude that both their representation by principal components (called "eigenvectorial" in their paper) and the dendrogram "fail to show the close recent relationship between BC and C" (two Makiritare villages). Looking at their own eigenvectorial representation (their fig. 1), I notice that BD and C are fairly close, although they are not closest. It is true, however, that *their* "dendrogram" sharply separates BD and C. These authors do not comment on the fact that the earlier analysis of the same data by Ward and Neel [26] had shown, instead, that BD and C are very close in the dendrogram (see the lowest diagram in Ward and Neel's fig. 2). Why are Lalouel and Morton unable to put together BD and C in their tree, when Ward and Neel had no problem?

There are differences in the two analyses: (1) Lalouel and Morton [45] use a new "hybridity" coefficient to measure genetic distance whereas Ward and Neel

[26] used one of the coefficients suggested by Edwards and myself; and (2) Lalouel and Morton use a new method of their own to reconstruct the tree while Ward and Neel used minimum path. Incidentally, Kidd and Sgaramella-Zonta [56] retested the same data by the method using least squares (the additive model) and reached essentially the same conclusions as Ward and Neel.

The measure of distance used by Lalouel and Morton could be at fault. They find that "there is gross similarity between the two indices" (their "hybridity" and the distance used by Ward and Neel). But in checking their table 2 [45], the correlation between the two indices is .942, which is perhaps more than a gross similarity. Actually, the relationship expected between the two indices is not linear, but obviously close enough to it in the range of this sample. What is at fault more is perhaps Lalouel and Morton's method of constructing a dendrogram. This method imposes the choice of the two nearest populations, which happen to be BD and E, as the starting pair for reconstructing the tree and leaves no leeway for later correction. This restriction is true of most "agglomerative" methods for building trees which start from the pair of closest neighbors. The methods that we have introduced are, in essence, "divisive"; that is, they start splitting all the populations into two groups and so continue. They differ from agglomerative methods in that they take account also of the information about the distance of two populations, A and B, considering also differences between A and C, B and C, etc.

The case cited may be, of course, just one example of failure of one agglomerative method. Agglomerative methods are, on the average, not as bad. A conclusion that I draw is that at the present state of the art one must always take the minimum caution of testing an adequate sample of trees, not just the single one reconstructed by the agglomerative method. Trees can then be tested by some reasonable measure of their goodness of fit. This is what we have built into our methods. The methodology is still far from perfect but it is perhaps more constructive to improve on it than to go back to methods that ignore the specific issue of phylogenesis, ask if they give information on it, and once they do not perform satisfactorily, declare the issue hopeless.

One final caution on the use of trees even if only for purely descriptive purposes: the trees shown in figure 1 are all topologically equivalent, but because of the

FIG. 1

different geometric ordering of the populations, they convey widely different impressions. We have found it useful to order the populations so as to have a high (possibly the highest) rank correlation with the first principal component. One could also space the populations accordingly. This adds to a tree representation

almost all the information that eigenvectorial methods can contribute with one dimension.

Trees may have taken an inordinate amount of space in this article, undoubtedly for personal reasons. I have found, in public and private discussions, that there are some widespread misconceptions and felt that this was a useful opportunity for clarifying some of them.

INBREEDING AND OUTBREEDING

One classical field of investigation of population structure has been the study of consanguinity and its effects. In general, bias for or against certain consanguineous marriages seems to be characteristic of most societies. Many of the social customs that have determined such behavior seem to have disappeared or to be disappearing. Thus, in Japan the preference for close consanguineous mating seems to be on its way out, judging from the decrease of isonymy of marriages in the last two generations [57]. On the other hand, the increase of close consanguineous marriages observed since the beginning of the last century in Roman Catholic countries [58, 59] has brought their frequency close to expectation in the absence of bias, at least in some areas [19].

When social customs are changing, the picture that may emerge is especially complex, since the process of change is often different in different social layers. Even if there is no change, a social stratification is expected because of the variety of customs in various social strata (or castes, when these exist). Traits that are more easily influenced by socioeconomic conditions, such as mortality, fertility, and most anthropometric or psychometric characters, are very likely to show a complex confounding of socioeconomic status (SES) and truly genetic effects of consanguinity. The complexity of the confounding shows especially well in the Hirado study [8] where rural and urban populations give an opposite regression of consanguinity with SES.

Can multiple regression really remove such effects and make the interpretation of the conclusions free from socioeconomic biases? It can, only if all the variables that may matter have been taken into account. This imposes on the research worker a considerable burden of detailed sociometric analysis, which is or was not customary, and always leaves room for doubt that all the important social variables were included. It remains likely that the use of sibling controls is the best procedure, but Schull and Neel [8] state that the study of SES is still necessary. One can add to their considerations the fact that different degrees of consanguineous matings show, at least in some areas, a widely different rural-urban distribution. Sibling controls may, apart from the objection raised by Schull and Neel, make more rigorous the comparison of a certain type of consanguineous mating with its control. But it does not help in the comparison of, say, second-cousin matings with first-cousin matings, at least not in the way it has been used so far. When studying third cousins in Parma for anthropometric characters [60], a totally unexpected but unquestionable increase in body size of their progeny was found over both controls and other inbreds which certainly could not be justi-

fied by genetic considerations. Using all SES differences available, part of this unexpected effect, but not all, could be explained. Third-cousin matings seemed to stand out as a unique class in this material. They are not very informative genetically, and might be left out, but the problem remains of how much the effect detected for them carries over to closer consanguineous matings.

It is difficult to say how much the criticism that SES effects are not usually accounted for may alter the conclusions that have been reached so far. In any case, the estimated consanguinity effects have so far proved difficult to interpret at other levels. Their interpretation value as proving a preponderance of the "mutational load" over the "segregational" one is certainly open to question (summaries in [12, 61]). Perhaps more confidence can be placed in the fact that one can derive from them estimates of "equivalent lethals," although it is not known today which fraction is mutational and which is segregational. Probably the major challenge to this interpretation may come from the possibility that a third fraction of unknown magnitude has to be carved out of the estimate of equivalent lethals to account for a third component, threshold effects.

Threshold effects have become popular after Falconer's paper in which he used a threshold and a polygenic model to account for the inheritance of diabetes [62]. Schull and Neel [61] feel that this approach is derived historically from the "phenodeviants," or more exactly, from Lerner's genetic theory of homeostasis [63]. This may be right, but then we have many different conflicting hypotheses together. The following facts seem worth attention.

1. Phenodeviants are found in highly inbred experimental animals; the degree of inbreeding reached there is one order of magnitude higher than that on which most human data on inbreeding are based. In spite of the greater chances of analysis offered by experimentation, they are not well understood even in experimental animals. This does not, probably, justify their classification of "mystical" [64], but it certainly decreases their usefulness in interpretations by analogy.

2. When a threshold theory is applied to data on inheritance of a character, it is very difficult to distinguish even between a polygenic and a one-gene interpretation. A one-gene theory assuming the same distribution of liability for each genotype and a threshold of manifestation is about as good (or as bad) as a polygenic theory with a threshold when applied, for instance, to data on schizophrenia [65, 66]. The chances of distinguishing between two hypotheses are small or nil by present techniques. They may be increased when two thresholds can be used, a less and a more severe one [67]. But with mortality the threshold is only one!

3. A multiple homozygosis theory, "specific" or relatively "nonspecific" as given by Schull and Neel, gives expectations different from that of a threshold theory, polygenic or not. It is unlikely, however, that with human data one can choose among all these theories.

Schull and Neel [8] correctly surmise that the study of outbreeding can usefully complement the study of inbreeding and provide expectations which could be verified. They cite three studies which have given contradictory conclusions. More could be cited at the anthropometric level indicating, for instance, heterosis

for stature; but they all suffer from lack of control of SES which obviously should be as close in these studies as for inbreeding analysis. It is difficult to believe, in any case, that outbreeding studies can offer better evidence for or against the phenodeviant hypothesis. As Schull and Neel themselves note, the existence of differences in gene frequencies for standard recessive diseases between populations will create heterosis effects. For each disease, one can compute that the heterotic effect will be small, probably beyond the chance of detection. Thus, taking the extreme example of Tay-Sachs disease, where gene frequency differences are favorable for this type of test, in F_1 matings between Jews and non-Jews, the frequency of those affected should be approximately $q_1q_2 = 1/50{,}000$, instead of the $(q_1 + q_2)^2/4 = 1/20{,}000$ expected in the F_2 or at equilibrium, where q_1 and q_2 are the gene frequencies in the two groups (.013 and .00015) [68]. Even in this case, the outbreeding effect is very small. It may be detectable when summing over all causes of morbidity and death, but present information is still contradictory.

Other ways of increasing returns in this type of research may also be considered. Better use could be made of the knowledge that has accumulated from anthropological observations. Uncle-niece matings give twice as much information on inbreeding as first cousins. In most populations they are exceedingly rare or absent, but in others they are frequent. In large segments of the Andhra Pradesh population in India, these matings are in excess of 10% [69]. In Sicily, in the last 30 years there occurred about 1,500 uncle-niece matings (A. Moroni et al., unpublished data).

A way of making the study of inbreeding or outbreeding more rigorous is to make it fully prospective. Fertility could then be studied more accurately by tests of early abortions in "missed periods." Mortality and its causes as well as other traits could also be analyzed more satisfactorily. It is only at the end of an investigation that one knows how it should have been planned. The accumulated experience may by now permit a better planning of future research, but it also shows that the effects to be expected in both inbreeding and outbreeding studies are small and demand large-scale investigations, with the added complication that a very careful control of socioeconomic conditions is necessary. The distinction between interpretations that involve only slightly different expectations does not seem to have much of a chance. But the required number of observations could, perhaps, be predicted to some degree of approximation.

HUMAN POPULATION GENETICS AND ANTHROPOLOGY

Anthropological information is a vastly untapped source of "experiments of nature" that may be useful to geneticists. We have seen a few examples with respect to inbreeding. I wish to cite another with respect to adoptions. The study of adopted children is important in understanding the inheritance of behavior where the environment inevitably plays a substantial role. Adopted children are few, often biological parents are unknown, and there are all sorts of potential biases introduced by adopting agencies. But a social custom in rural Taiwan is

that a girl is very often adopted at an early age into another family to provide a future bride for the son of the adopting family. Naturally, such experiments of "nature" should, as with twins, be viewed with caution because they are full of traps. In the case of adoption of future brides in Taiwan, the study from which I learned about it [70] shows one of the inherent dangers. Marriages contracted with adopted sisters tend to last less long and produce fewer children than the "controls," indicating a greater likelihood of a psychological imbalance.

There are many other aspects in which anthropological information can be of direct use to genetics; for instance, populations which have been isolated from the rest of the world for a substantial time (and which are, still now, difficult to reach) may show an unusual wealth of new genetic variation not found or more difficult to find elsewhere.

The ties of human population genetics and anthropology are far deeper than these few examples indicate, and a great deal of cross-fertilization can occur from greater exchange. Among the many overlaps, I find the similarities, dissimilarities, and interactions of cultural and biological evolution an almost virgin field [71–75] and one that has great potential not only for the intellectual challenge that it offers, but also for a better understanding of human nature.

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Addendum

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