Meetings

Human Population Genetics

The Genetics Study Section of the National Institutes of Health sponsored a conference on Goals in Human Population Genetics at the University of Texas on 12 January 1966. The purpose of the conference was to review the research objectives of studies in human population genetics, with particular attention to what such studies hope to accomplish and to what extent present methodology is adequate for accomplishment.

The morning session, guided by H. B. Newcombe (Atomic Energy of Canada, Ltd.), considered the genetics of inbred populations. J. F. Crow (University of Wisconsin) began with the observation that perhaps the most spectacular result to be expected from the study of small, inbred human populations is the discovery of new, or the study of rare, diseases such as pyruvate kinase–deficient hemolytic anemia, dwarfism with Ellis–van Creveld syndrome or with cartilage-hair hypoplasia, and hydrometrocolpos in the Pennsylvania Amish investigated by Victor McKusick (Johns Hopkins University). Comparison of more than 200 autosomal recessives with the 50 X-linked recessives known in human populations suggests that something like 600 new autosomal recessives await discovery if the 22 pairs of autosomes (some 94 percent of the genome) have the same proportion of loci with recessive mutants as the X chromosome. Isolated, inbred human populations are an excellent source for discovery of the unknown three-fourths of "available" knowledge in this area of human genetics.

Crow suggested that some recent misunderstandings regarding the effects of random versus nonrandom inbreeding in human populations could be avoided by use of notations introduced by S. Wright in 1943. Let F be Wright's inbreeding coefficient (the correlation of uniting gametes or the probability that an inbred individual will be homozygous for alleles identical by descent) and let the subscripts I refer to individuals; S, to strains, isolates, or other subdivisions of the population; and T, to the total or base populations. Then F_{IT} is the inbreeding of individuals in an isolate with reference to the foundation population, F_{ST} is the inbreeding relative to the base population that would persist if random mating within the subpopulation were initiated, and F_{IS} is the inbreeding of an individual relative to the isolate. The correlation between random gametes from the same population, relative to the total, is given by

$$F_{ST} = (F_{IT} - F_{IS})/(1 - F_{IS})$$

where F_{ST} is necessarily positive but F_{IS} and F_{IT} can be negative.

Crow stressed several topics in which human populations provide poorer evidence in studies than do *Drosophila* or other experimental organisms. In *Drosophila* studies, the inbred load measured by lethal equivalents indicates that major genes are about twice as important as minor genes. Man is an unsuitable organism for study of the possible nonlinearity (because of epistasis or other interaction) of regressions on values of F, because the usable range of F in man is from 0 to 1/16; in *Drosophila*, values $0 \leq F \leq 1$ are available, and viability is nonlinear with higher values of F in that, on the average, interaction makes the double mutant slightly worse.

Crow reads the *Drosophila* data to mean that most lethals in natural populations are maintained by mutation and are slightly deleterious in heterozygotes. Theory demands, according to Crow, that if there are many polymorphisms maintained by selective advantage of heterozygotes the selection coefficients must be small on the average.

Richard Lewontin (University of Chicago) reported current *Drosophila* work at Chicago suggesting (in agreement with similar studies by R. Richardson, F. M. Johnson, W. S. Stone, and M. R. Wheeler at the University of Texas) that 30 to 40 percent or more of all loci are polymorphic. Barton Childs (Johns Hopkins University) and A. G. Bearn (Rockefeller University) suggested that it may well turn out that the majority of enzymes and serum proteins are polymorphic in human populations.

W. J. Schull (University of Michigan) discussed the results now available from study of inbred human populations. Inbreeding has been ascertained from church records, questioning of parents of school children, registration of pregnant women for food rationing, screening of migrants passing through a relocation center, and censuses. He emphasized work done in Japan where about 6 percent of all urban marriages are consanguineous.

The effect of inbreeding on populations is to increase the proportion of homozygous genotypes; such effects may be detected from differences between inbred and noninbred individuals in mortality, development, morbidity, and fertility, and by these kinds of differences in the children of inbred individuals. Controls used (Schull uses the less ambitious term "comparison groups") include sibs, nearest neighbors, and randomly selected individuals who are not inbred.

On the assumption that different genetic and environmental causes of death are independent, the survivors, S, to the reproductive period may be expressed

$$-\log_e S = A + BF$$

where F is the coefficient of inbreeding, A is a measure of the amount of expressed mortality from both genetic and nongenetic causes, and B is a measure of the hidden genetic damage that would be fully expressed only in complete homozygotes (whose $F = 1$).

Studies in four Japanese towns or cities (Hiroshima, Nagasaki, Shizuoka, and Hoshino) estimated values of B to range from 0.33 to 1.11 percent per 1 percent F, significant at the 5 percent level, leading to estimates of B/A from 1.08 to 10.57. These estimates of the ratio of the inbred to the random load in the four Japanese populations suggest that the load revealed by inbreeding may not be mostly mutational in origin; rather, the results are consistent with a substantial fraction of the load being segregational in origin.

Genetic load theory has been used to interpret data on inbred populations in Brazil, Israel, Japan, the United States, and several European countries. These studies reveal surprising varia-

tion in inbreeding effects regarding geographical region, rural-urban residence, race, birth order, samples for same race and area, and number of fetal deaths.

Newton Morton (University of Hawaii) felt that we do not know how to interpret these diverse findings in terms of a general theory; that studies of inbreeding should follow more-refined analysis, applying all available controls, including stratification, multivariate analysis of concomitant variation, matching of consanguineous parents with their sibs or neighbors, and more careful estimation of error variance among families rather than use of the common χ^2 test which treats sibs as independent events, whereas the phenotypes of sibs are correlated because of segregation frequencies which take values of 0, ¼, or ½ for unlinked genes.

Walter Bodmer (Stanford University) wanted more work done on the genetics of our own population; relatively inexpensive changes in procedures employed by the Census Bureau would enable interpretation of census data in terms of genetic parameters.

W. S. Laughlin (University of Wisconsin) opened the afternoon session on the genetics of primitive and isolate populations, with J. V. Neel (University of Michigan) in the chair. Laughlin and Neel pointed out that surviving hunting and gathering populations, until recently characterized by social isolation and stability, now face imminent breakdown of their culture, with far-reaching changes in their population biology as a result of contact with genes, germs, and gadgets from industrial societies. If the opportunity is not to be irretrievably lost, the remaining hunting and gathering populations in the Arctic, South America, Africa, Asia, and Australasia must be genetically studied immediately.

Laughlin emphasized that genetic study of such populations is the best possible research for investigation of the general kind of microevolutionary processes that prevailed during the initial 99 percent of the history of our species. An example of a little-understood but easily studied evolutionary situation is the contrast between the marked between-group genetic diversity of the Aleuts, occupying a linear zone stretching east-west some 1,250 miles, and the relative lack of genetic differentiation in the Eskimo populations living in a longer north-south linear strip on the west coast of Greenland.

Laughlin thought that the mobility of modern man leads population geneticists to overemphasize the importance of gene flow in our species during most of its history. Subgroup A_1 of the A-B-O blood groups is high in frequency among some Indians of North America; the Di^a gene is high in frequency among many Indians of South America; the absence or low frequencies of A_1 in South American and Di(a+) in North American Indian populations indicate a low rate of gene flow between the two hemispheres.

In the fourth and final prepared presentation, Morton spotlighted the fact that far more single genes with frequencies higher than 1 percent in natural populations are known in man than in any experimental form, including *Drosophila*. For the part of population genetics that tests theoretical models on the forces that change or maintain genotypic frequencies in breeding populations against empirical evidence, man in the mass is the organism of choice in at least three aspects of population genetics: segregation patterns, population structure, and genetic loads.

Not all human populations are equally suitable for a particular genetical problem on populations: small, isolated populations, important in some ways, are not good for the study of natural selection because they are too homogeneous. Hunters and gatherers are in some ways better for study than technologically advanced populations but are difficult regarding access, demographic records, comparability, and restriction to vague indices of selection.

In Brazil, stillbirths and neonatal mortality increase curvilinearly with increase in order of birth, the acceleration being positive when the mother is inbred and negative when the child is inbred. Morton thinks the load expressed under inbreeding is not independent of environmental factors, and these may interact in complex ways with genetic factors.

Morton traced the history of the genetic theory of population structure back to 1908 when Hardy and Weinberg showed that genotypic frequencies were the squares of the gene frequencies, with random mating. Starting in 1931, Wright developed deterministic models that included the effects of mutation, gene flow, selection, genetic drift, and the patterns of mating on the distribution of genotypes in populations; in 1943 and later he assumed a bivariate normal distribution of distances between birthplaces of parents and their children and an assignable neighborhood size, with mating random with regard to consanguinity. Dahlberg in 1929 had developed the notion of isolate size estimated from the observed frequency of any type of inbred matings, but had not deduced any relation between isolate size and genotypic frequencies. In 1928 Wahlund discovered that gene and genotypic frequencies were a function of the genetic variance among local populations. Wright (1943) showed that this variance is a function of gene frequencies, q, and the amount of inbreeding, F, so that genotype frequencies (neglecting selection, or counting genes before the operation of selection) are a function of q and F only. Malecot (1948, 1963) expressed the relationship of mates as a function of distance between their birthplaces, if one assumed normal or stepping-stone dispersal. An exponential distribution of distances developed by Kimura (1963) shows a good fit to human data. Morton and Yasuda (1963) discovered how to estimate F caused by local differentiation by use of either frequencies of polymorphism or marital distances for parents of rare homozygotes. Yasuda (1964) extended Wahlund's method to give mating-type frequencies as a function of q and F (neglecting third and fourth moments of q).

All attendees agreed that the intrinsic anthropological interest and importance of the genetics of small, isolated human populations justified their study on a broad scale, even though the cost per unit of genetic information is higher than for, say, *Drosophila* studies. There was difference of opinion on the general genetic value of studying isolated human populations. Men who work mostly with nonhuman organisms (that is, most experimental and theoretical geneticists) considered that the results of such studies—although of admitted anthropological interest—are not of great consequence for the general genetic theory of evolution; most of those who work mainly or extensively with human populations felt that man is the organism of choice for the study of several large and general areas of population genetics. For some problems, the study of isolates and of local groups of hunters and gatherers is ideal; if they are to be studied at all, the work must start soon.

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