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The Pool of Harmful Genes in Human Populations

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The concepts of dominance and recessivity as applied to human genetical traits are losing their original connotations. It is better to speak of genes unconditionally deleterious in heterozygote form and those for which such disadvantage is doubtful. The classical dominant traits come into the first category and in the large majority they give rise to grossly pathological conditions and are ipso facto harmful-many in fact are lethal. In the case of these genes it is difficult to conceive that any agency other than recurrent mutation is instrumental in keeping them at their present frequency.

Assuming that such mutation rates are of the same order of magnitude over the entire spectrum, the frequency of these traits will vary inversely with their severity and this is found to be approximately true-from an incidence of 3/million for an almost invariably lethal trait such as acrocephalosyndactyly to 1/1000 for a relatively innocuous trait such as ptosis.

We would not expect genes even at the higher of these frequencies to be often seen and recognised in homozygote form with the low degree of inbreeding prevalent in human populations. This is in fact confirmed in practice and examples of possibly homozygous forms ot dominant conditions are very rare. To be recognized as causing a recessive trait, with a few exceptions in inbred communities, a gene must be more common and often cannot therefore be maintained by recurrent mutation alone. Very wide geographical variations in the incidence of such traits also militate against such an interpretation. Phenylketonuria is an excellent example. The abnormal gene reaches a frequency of as much as 1% in some populations and it is unknown in others.

Of recent years a very plausible theory has benn evolved to explain the great prevalence of various abnormal haemoglobin forms, in some African, Asian, and Mediterranean populations. It has been suggested that in heterozygous form these genes confer an advantage in resisting the depredations of malaria. This is an excellent illustration of the concept of a balanced polymorphism by an advantage of a heterozygote over both homozygotes. It may well be that similar mechanisms, which need not necessarily be still acting now, but which may have been operative in the remote past, are responsible for the present day distribution of many specific recessive traits.

Contrary to what is known of experimental animals, these recessive traits form only a small proportion of the total of segregating traits known in Man. This is merely an accident of observational bias and stems from our very different approach to problems affecting our own species.

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Thus the genes causing many of the dominant traits in Man would not be recognised in heterozygous form in drosophila and, because of the very close inbreeding in laboratory populations, would make their appearance as recessive lethals or semi-lethals. In our species the boundaries between dominance and recessivity are fast breaking down as refinements of techniques are enabling us to detect more and more genes in heterozygous form, previously recognized only in homozygotes. It would be impracticable at the present time, on the other hand, to detect a mouse or fruit fly heterozygous for phenylketonuria.

Sex-linked traits occupy a somewhat special position. In this situation acuity of observation does not introduce a bias in favour of detecting dominant rather than recessive conditions and the proportion of the two approaches far more closely that found in experimental animals. While in cases of some grossly deleterious sex-linked conditions such as haemophilia and muscular dystrophy it has been supposed that the mutant genes involved are maintained only by recurrent mutations, the rates calculated on this hypothesis are somewhat high and the possibility of heterozygote advantage in the female cannot be excluded. This is true especially of a condition such as glucose-6-phosphate dehydrogenase deficiency whose high frequency and unequal geographical distribution suggests that it is another of the traits which owes its existence to heterozygote advantage vis à vis the malaria parasite.

It is not possible in the present context to give an exhaustive catalogue of genes which cause dominant, recessive, and sex-linked harmful conditions. It appears that the mechanisms responsible for the maintenance of these genes are complex in the extreme. Recurrent mutation and heterozygote advantage are only two of the simpler hypotheses, and at any locus it is extremely difficult to say which is mainly responsible.

There is in addition to these classical genetical traits a very large body of variation whose complexities are only recently becoming apparent. These include the blood groups and the serum protein and drug sensitivity polymorphisms. Only in a few cases is the selective value of any of these variants apparent. The recent work on the association of blood groups with disease is suggestive. The presumptive advantage of glucose-6-phosphate dehydrogenase deficiency heterozygotes in malarious areas has already been mentioned and this polymorphism may present as a drug sensitivity. In some cases the mechanisms involved are more subtle. It is not easy to explain selection against Rhesus D heterozygotes by haemolytic disease of the newborn. The dichotomy between historical and biological time must be remembered in this context. It may be that this situation reflects the result of comparatively recent migratory movements of populations whose genetical structure became different due either to selection or chance fixation by drift. Whatever the mechanisms involved there can be no question of the harmfulness of such variation in the individual families affected.

Muller has suggested that in Man there are about 5000 loci capable of separate non-allelically expressed mutation. We have already considered briefly several hundred of these and as yet only scratched the surface of human variation. Many of its most important manifestations such as viability expressed in terms of abortion, stillbirth, congenital malformations, neonatal and juvenile deaths and infertility, intelligence and resistance to infectious disease are not as yet amenable to simple genetical analysis. The important influence of genetical factors in these basic components of Man's biological structure, however, can scarcely be doubted. Studies of the results of inbreeding may contribute towards unravelling this. Theo-

retical formulations derived for these studies have also been applied to conditions with a complex but more clearly discernible genetical basis such as deaf-mutism, mental deficiency and muscular dystrophy. In conjunction with careful clinical and laboratory evaluations this corpus of theory could be of great value in further studies of such entities.

Recent advances in the cytological definition of the human chromosomes have led to another possible avenue of exploring complex genetical situations. This approach has already been extremely fruitful, as, for example, in the study of a very common congenital malformation, mongolism, and promises much for the future. Under certain circumstances chromosomal re-arrangements can lead to Mendelian segregations; under others they can simulate them closely. While the type of trisomy giving rise to mongolism is clearly unconditionally harmful, other more subtle aberrations, some of which may be beyound detection by present day techniques may be kept in being by much the same type of mechanism as polymorphisms involving simpler genic mutations. We know that this is a very common phenomenon in drosophila and it may be that the karyotype of Man is also relatively inconstant.

It is difficult to escape the conclusion that in a free breeding population, spread over the entire surface of the world, a large proportion of the genetical material of Man is in fact heterogeneous. Recently a concept has been lauched of a genetical load of a species as the proportion by which its fitness at any locus is decreased by comparison with the optimum genotype. This would imply that all variation is harmful and in fact the term substitutional load has been coined to cover the failure to achieve optimum fitness even during the period that a newly arisen and unconditionally favourable allele is ousting the original one. This seems a reductio ad absurdum but it may be that the difficulty is a semantic one and the word load is being interpreted too literally. The concept remains very useful theoretically but variation per se cannot be equated with genetical detriment.

The situation is far more difficult and it is not possible to extrapolate from deductions derived from isolated epiphenomena to deductions involving the incredible complexity of the whole genotype. Mutation is the building stuff of evolution; the many successaful results are the price a species has to pay for the privilege of being able to use the rarer good material. Segregation is a method in a sexually breeding species of conserving variation; it is the means whereby it can store adaptability and be prepared to colonize any environment which offers opportunities for expansion, or, in unfavourable circumstances, for survival. Nor is the optimum genotype an absolute ideal. In a species such as our own which occupies many diverse niches a genotype may be optimum in some circumstances but not in others. Thus heterozygosity for the Haemoglobin gene (sickling trait) may be optimum in Africa but not in England. Such differences in optimum may be secular as well as geographical and this fact is of some practical importance. Thus, for example, the dysgenic effects of modern medical practice in preserving inferior genotypes have frequently been pointed out. What has been pointed out less frequently is the very great reduction in a few generations in the frequency of the sickling gene in American negroes as compared to their African cousins. When malaria is wiped out it may be expected that the incidence of sickling in Africa will be reduced likewise.

Various attempts at a synthesis of these epiphenomena have been made. Among the most notable are those of Waddington (1957) and Lerner (1954). To the latter we owe the conception that many unfortunate accidents of nature are ' phenodeviants ', the price the species pays

for failing to keep the level of ' obligate heterozygosity '. To Kimura (1960) we owe the concept of optimum mutation rate as determined by minimum genetical lead. Thus it is seen that both mutation and segregation are regarded, whether viewed at single loci in isolation or in any form of synthesis (and it must be remembered that even these sophistications reveal only a fraction of the complexity of the organization of hereditary matter), as necessary evils. While it is not denied that individuals, families and sometimes entire nations have to pay a very heavy socio-economic price, a genetical load is something which no species, least of all man, will ever be without. We can only strive to keep it to the minimum; the ideal homozygote will never be found. This is not a philosophy of despair nor a licence to relax all precautions. Thus for example, a species is adapted to the mutation rate existing at the epoch and an abrupt change can have no consequences for the good. The complexity of the genetical dynamics of a population can be compared to the complexity of the molecular organization of a cell. Yet just as a cell functions as a beautifully integrated whole so does the total genetical constitution of a population; and just as a cell is sensitive to a variety of insults so is the hereditary material of our species to any uncontrolled changes in its environment.

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