

Annotation

Heterozygote advantage

Genic disorders, by definition, impair health and where children are affected the prospect of reproduction. When the disorder is only manifest if there are offending alleles at both loci, as in fibrocystic disease—the commonest recessive disease of Anglo-Saxons, or thalassaemia, the commonest in the world—there is a loss of two abnormal alleles with each affected birth since the homozygotes rarely reproduce. How is this loss compensated? In the United Kingdom 10 years ago there were almost a million births a year in a population of 50 millions. Each year about 500 children die with fibrocystic disease, diminishing the gene pool by 1000 alleles. Since in a recessive disease the gene frequency is, excluding small corrections for cousin marriages and other forms of inbreeding, the square root of the incidence, that is $1/\sqrt{2000}$, or $1/45$, about one person in 22 is a carrier, and in a million births we expect 45 000 carriers. Clearly these could make good the losses if they provided more than the average number of children. As half their children would be carriers, they would merely need to have a relative fertility of $(22\ 500 + 1000)/22\ 500$, or an increment of 4.4% to break even. The present birth rate is now far less, but this makes the arithmetic more difficult and does not affect the argument.

To put it in symbolic terms, pairs of gametes carrying alleles P or Q in proportions p and q, unite in proportions p^2 , $2pq$, and q^2 . The rarer homozygote has two Q alleles, so the proportion lost each generation is $2q^2/(2pq + 2q^2)$ which is q. Since q^2 is the incidence of disease, the proportion of abnormal genes would 'deflate' at an interest rate of $-q$ per generation, the disease declining in incidence by $2q$ per generation unless maintained by some mechanism.

How could some 50 000 alleles, which can only survive to convey themselves in effective gametes if they have a normal allelic partner, become established in the British Isles—and how have some half a million or more got into the world currency? There are four possibilities. First, suppose our ancestors were exposed to the sort of numerical isthmus due to having come from a small roving band who founded, or conquered, some area. If there were n founders who would have 2n loci, then the frequency of any abnormal alleles in these

founders must be $0/2n$, $1/2n$, etc. If, for example, 500 Israelites crossed the Red Sea, then the gene frequencies would necessarily be zero or at least $1/1000$ and, since many would be in family groups, even the rarest alleles would usually be present in more than one person. Such migrations and settlements involve the proportion of defective alleles at all loci being conserved, but their variety being decreased.

Suppose that some effective group of founders had, by chance, a hundred individuals, 20 of whom were heterozygotes, and increased over 10 000 years to 100 000 000. The question is not easy due to miscegenation, the capture of women who would not be related to the founder carrier, and other realities which confound arithmetic. However, with random mating the half-life of an allele which does not reproduce in the homozygote (genetic lethal) which has a gene frequency of 5% is 15 generations, or only about 400 years, so that a founder effect will not explain such a common disease in Britain.

Secondly, there could be a general tendency due to some advantage in health or vitality, or in the capacity to conceive, carry, deliver, or rear, and could be manifest by disease resistance, cold resistance, and by any number of physical or psychological mechanisms. If there were some simple immunity to some disease, then a vast survey of sibs and parents might reveal some peculiarity: however, the selective advantage, if it existed, was spread over several millenia when disease experience was very different and survival in infancy was far more dependent on the mother as a source of both milk and heat. Little seems to be known of milk secretion in heterozygotes, though some slight increase in sodium and chloride would seem likely. The heterozygote does not seem to differ in any way from the normal, apart from a tendency to induce chaotic movements in such tissues as the trachea of rabbits¹ and the gills of the Texas oyster,² an aptitude not reflected by respiratory disease in heterozygotes. This could obviously be advantageous if it were to immobilize ciliated or flagellated protozoa, or possibly motile bacteria.

In the commonest recessive lethal, thalassaemia, there is good evidence that heterozygotes are protected from malaria; protection is also more evident, and possibly stronger, in sickle cell anaemia. In

both conditions the heterozygote has hardly any handicap without exposure to malaria, and considerable advantages if exposed. The advantages of the sickle cell mutant are sufficient for the entire population of sicklers to have had a common ancestor in early post-Christian times.³ This is consistent with the virtual absence of sickling, though not of thalassaemia, in Britain since the Roman Army of occupation which doubtless included both Greeks and Negroes. Septimus Severus, the only Negro emperor, is reported to have lost 20 000 troops in a punitive expedition against the Scots in 208 AD⁴ when the standing army of occupation must have been several per cent of the population.

At present there is no evidence of any advantage to carriers of fibrocystic disease. However, evidence of *under-representation* of any disease is very difficult to obtain. The average paediatrician covering a population with less than 4000 births a year, will see one or two new cases a year, or some 50 a lifetime. Even the most astute clinician is hardly going to find a meaningful lack of any specific disease among an unknown half of the 200 grandparents of 50 fibrocystics. Direct evidence of increased family size among the grandparents is consistent with this,⁵ though there are grave statistical difficulties in such comparisons.

Thirdly, there may be 'compensation'—that is the death of an infant may lead to replacement as a result of which the replacing sib, if surviving, would have a 2/3 chance of being a carrier. If such deaths lead to 50% increase in surviving children, then the disability would be stable. This mechanism would only come into play when the gene frequency was high enough for recessives to become an appreciable cause of death. Even then, the extent of the compensation necessary is unrealistic.

Fourthly, the disease may be maintained by mutation. This seems most unlikely; the mutation rate necessary would be far too high for a simple genic element to be responsible, and the extreme racial variation found would not arise. Mutation is unlikely to be responsible for more than a few new defective

alleles a year per million births, or to replace more than a hundredth of those lost by death in childhood. In practice, mutation as an immediate cause of autosomal recessive disease can be disregarded.

Of the four possibilities, three are unrealistic, so that substantial selective advantage of heterozygotes over the last few hundred years must be postulated. If the advantage were restricted to earlier times, then realistic incidences of the disease might be expected to have dropped to below the present level.

From the practical point of view, parents who are concerned at either being carriers, or of their healthy children being carriers, can be assured that they are as fit, if not fitter, than average, and that they have no responsibility to reduce the number of carriers. Abortion after fetal diagnosis, which might reasonably be anticipated within a decade, should be restricted to homozygotes. And, finally, further posters by charities about the high frequency of carriers should be more carefully worded in order to avoid the leprous connotation which is so easily conveyed to the disadvantage of both parents and sibs. Heterozygote advantage is difficult to explain but unwise to destroy.

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