THE COST OF NATURAL SELECTION

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Introduction

It is well known that breeders find difficulty in selecting simultaneously for all the qualities desired in a stock of animals or plants. This is partly due to the fact that it may be impossible to secure the desired phenotype with the genes available. But, in addition, especially in slowly breeding animals such as cattle, one cannot cull even half the females, even though only one in a hundred of them combines the various qualities desired.

The situation with respect to natural selection is comparable. Kermack (1954) showed that characters which are positively correlated in time may be negatively correlated at any particular horizon. The genes available do not allow the production of organisms which are advanced in respect of both characters. In this paper I shall try to make quantitative the fairly obvious statement that natural selection cannot occur with great intensity for a number of characters at once unless they happen to be controlled by the same genes.

Consider a well-investigated example of natural selection, the spread of the dominant *carbonaria* gene through the population of *Biston betularia* in a large area of England (Kettlewell, 1956*a*, *b*). Until about 1800 the original light type, which is inconspicuous against a background of pale lichens, was fitter than the mutant *carbonaria* due to a gene **C**. Then, as a result of smoke pollution, lichens were killed in industrial regions, and the tree trunks on which the moths rest during the day were more or less completely blackened. The **cc** moths became more conspicuous than **Cc** or **CC** and the frequency of the gene **C** increased, so that **cc** moths are now rare in polluted areas. During the process of selection a great many **cc** moths were eaten by birds. Kettlewell (1956*b*) showed that the frequency of the more conspicuous phenotype may be halved in a single day.

Now if the change of environment had been so radical that ten other independently inherited characters had been subject to selection of the same intensity as that for colour, only $(\frac{1}{2})^{10}$, or one in 1024, of the original genotype would have survived. The species would presumably have become extinct. On the other hand, it could well have survived ten selective episodes of comparable intensity occurring in different centuries. We see, then, that natural selection must not be too intense. In what follows I shall try to estimate the effect of natural selection in depressing the fitness of a species.

The principal unit process in evolution is the substitution of one gene for another at the same locus. The substitution of a new gene order, a duplication, a deficiency, and so on, is a formally similar process. For the new order behaves as a unit like a gene in inheritance. The substitution of a maternally inherited self-reproducing cytoplasmic factor by a different such factor is formally similar to the substitution of a gene by another gene in a haploid or of a gene pair by another gene pair in a self-fertilized diploid. I shall show that the number of deaths needed to carry out this unit process by selective survival is independent of the intensity of selection over a wide range.

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Natural selection may be defined as follows in a population where generations are separate. The animals in a population are classified as early as possible in their life cycle for phenotypic characters or for genotypes. Some of them become parents of the next generation. A fictitious population of parents is then constituted, in which a parent of n progeny (counted at the same age as the previous generation) is counted n times. If the sex ratio is not unity a suitable correction must be made. If generations overlap Fisher's (1930) reproductive value can be used instead of a count of offspring. Natural selection is a statement of the fact that the fictitious parental population differs significantly from the population from which it was drawn. For example, with respect to any particular metrical character it may differ as regards the mean, variance, and other moments. A difference in means is called a selective differential (Lush, 1954).

Selection may be genotypic or phenotypic. Phenotypic selection may or may not result in genotypic selection. By definition it does not do so in a pure line. Nor need it do so in a genetically heterogeneous population. If underfed individuals are smaller than the mean, and also on an average yield less progeny as a result of premature death or infertility, there is phenotypic selection against small size. But this could be associated with genotypic selection for small size, if organisms whose genotypes disposed them to small size were less damaged by hunger.

In what follows I shall consider genotypic selection; that is to say, selection in which some genotypes are more frequent in the parental population than in the population from which it was drawn.

We can measure the intensity of natural selection as follows. First let us consider selection by juvenile survival. For any range of phenotypes there is a phenotype with optimal survival, s_0, compared with S in the whole population, and similarly for a range of genotypes which includes the whole population. The intensity of selection is defined (Haldane, 1954) as $I = \ln(s_0/S)$. Thus Karn & Penrose (1951) found that about 95·5 % of all babies born in a London district and 98·5 % of those weighing 7·5–8·5 lb. survived birth and the first month of life: $s_0 = 0{\cdot}985$, $S = 0{\cdot}955$, $I = 0{\cdot}03$. The notion is even simpler for genotypes where they can in fact be distinguished. If all genotypes had survived as well as the optimal genotype, s_0 individuals would have survived for every S which did so. That is to say, of the $1-S$ deaths, $s_0 - S$ were selective. When s_0 and S are nearly equal, $I = s_0 - S$ approximately.

If selection is measured by comparing the parental population with the one from which it is derived, suppose that a number of genotypes are distinguished. Let f_r be the frequency of the rth genotype in the original population, F_r its frequency in the parental population:

$$\Sigma f_r = \Sigma F_r = 1.$$

Let $F_r f_r^{-1}$ be maximal when $r = 0$. The 0th genotype is called the optimal. If all genotypes had been as well represented in the parental population it would have contained $F_0 f_0^{-1}$ individuals for every one which it contained in fact. Thus the intensity of selection is $I = \ln(F_0/f_0)$.

It is convenient to think of natural selection provisionally in terms of juvenile deaths. If it acts in this way, by killing off the less fit genotypes, we shall calculate how many must be killed while a new gene is spreading through a population. This supplements my earlier calculation (Haldane, 1937) as to the effect of variation on fitness. I pointed out that, in a stable population, genetic variation was mainly due to mutation and to the

lesser fitness of homozygotes at certain loci. I calculated that each of these agencies might lower the mean fitness of a species by about 5–10%. In fact the effect of sublethal homozygotes is much greater than this in such organisms as *Drosophila subobscura* and *D. pseudo-obscura*. I did not deal with the dynamic effect of Darwinian natural selection in lowering fitness.

Loss of fitness in genotypes whose frequency is being lowered by natural selection will have different effects on the population according to the stage of the life cycle at which it occurs, and the ecology of the species concerned. In some species the failure of a few eggs or seeds to develop will have little effect on the capacity of the species for increase. This is perhaps most obvious in such polytokous animals as mice, where a considerable prenatal elimination occurs even when no lethal or sublethal genes are segregating. But we can judge of the effect of elimination of a fraction of seeds from Salisbury's (1942, p. 231) conclusion that 'for ecologically comparable species, the magnitude of the reproductive capacity is associated with the frequency and abundance of which it is probably one of the determining factors'. Failure to germinate lowers the reproductive capacity. But death or sterility at a later stage is probably more serious in species whose members compete with one another for food, space, light and so on, or where overcrowding favours the prevalence of disease.

Natural selection, or any other agency which lowers viability or fertility, lowers the reproductive capacity of a species. This is sometimes called its 'natural rate of increase', but this expression is unfortunate, since in nature a population very rarely increases at this rate. Haldane (1956*a*) pointed out that in those parts of its habitat where climate, food, and so on are optimal, the density of a species is usually controlled by negative density-dependent factors, such as disease promoted by overcrowding, competition for food, and space, and so on. In such areas a moderate fall in reproductive capacity has little effect on the density. In exceptional cases, such as control by a parasite affecting no other species, it can even increase the density (Nicholson & Bailey, 1935). But in the parts of the habitat where the population is mainly regulated by density-independent factors such as temperature and salinity, the species can only maintain its numbers by utilizing its reproductive capacity to the full. A fall in reproductive capacity will lead to the disappearance of a species in these marginal areas, except in so far as it is kept up by migration from crowded areas. Birch (1954) showed very clearly that in some cases species with a similar ecology compete on the basis of their reproductive capacities.

It must, however, be emphasized that natural selection against density-independent factors is quite efficient in populations controlled by density-dependent factors. If in some parts of its range *Biston betularia* is so common as to be controlled mainly by parasites favoured by overcrowding, selective predation is not abolished. If 90% of the larvae die of disease, the 10% of imagines which emerge are still liable to be eaten by birds. Negative density-dependent factors must, however, slightly lower the overall efficiency of natural selection in a heterogeneous environment. If as the result of larval disease due to overcrowding the density is not appreciably higher in a wood containing mainly *carbonaria* than in a wood containing the original type, the spread of the gene C by migration is somewhat diminished.

A serious complication arises in bisexual organisms if the selective killing or sterilization is of different intensity in the two sexes. In any particular species and environment

there is presumably an optimal sex ratio which would give the most rapid possible rate of increase. This would be near equality for monogamous animals, whereas an excess of females might be optimal where a male can mate with many females. But if males are smaller than females or have to search for them intensively an excess of males might be optimal. There is little reason to think that the sex ratio found in nature is closely adjusted to the optimum.

In a species with considerable embryonic or larval competition, and an excess of males above the optimum, the early death of some males might be advantageous. But even in this case an increased death-rate of males soon before maturity or during maturity would be of no advantage. Before dying they would have eaten the food which might have nourished other members of the species, and would have infected them, and so on. There seems no good reason why natural selection should fall more heavily on males than on females except in so far as males are haploid or hemizygous. But even if it fell wholly on males, it would not in general be harmless to the species.

I shall investigate the following case mathematically. A population is in equilibrium under selection and mutation. One or more genes are rare because their appearance by mutation is balanced by natural selection. A sudden change occurs in the environment, for example, pollution by smoke, a change of climate, the introduction of a new food source, predator, or pathogen, and above all migration to a new habitat. It will be shown later that the general conclusions are not affected if the change is slow. The species is less adapted to the new environment, and its reproductive capacity is lowered. It is gradually improved as the result of natural selection. But meanwhile a number of deaths, or their equivalents in lowered fertility, have occurred. If selection at the ith selected locus is responsible for d_i of these deaths in any generation the reproductive capacity of the species will be $\Pi(1-d_i)$ of that of the optimal genotype, or $\exp(-\Sigma d_i)$ nearly, if every d_i is small. Thus the intensity of selection approximates to Σd_i.

Let D_i be the sum of the values of d_i over all generations of selection, neglecting the very small values when the eliminated gene is only kept in being by mutation. I shall show that D_i depends mainly on p_0, the small frequency, at the time when selection begins, of the gene subsequently favoured by natural selection. I shall assume that the frequency of the phenotype first kept rare, and later favoured, by natural selection is about 10^{-4}, a value typical for disadvantageous but not lethal human phenotypes. If so p_0 would be about 5×10^{-5} for a partially or wholly dominant gene, and about 0·01 for a fully recessive one. The former are probably the more important in evolution. All the known genes responsible for industrial melanism are at least partially dominant, and most gene pairs which are responsible for variation of metrical characters in natural populations (as opposed to laboratory or 'fancy' mutants) seem to give heterozygotes intermediate between the homozygotes.

Selection in haploid, clonal, or self-fertilizing organisms, or for maternally inherited cytoplasmic characters

Let the nth generation, before selection, occur in the frequencies

$$p_n\mathbf{A}, q_n\mathbf{a}, \quad \text{where} \quad p_n + q_n = 1.$$

Here **A** and **a** are allelomorphic genes in a haploid, genotypes in clonal or self-fertilizing

organisms, or different types of cytoplasm. If $1-k$ of **a** survive for every one of **A**, then the fraction of selective deaths in the nth generation is

$$d_n = kq_n. \tag{1}$$

Also
$$q_{n+1} = \frac{(1-k)\,q_n}{1-kq_n}.$$

So
$$\Delta q_n = \frac{-kp_n q_n}{1-kq_n}. \tag{2}$$

Hence $q_n = [1+(1-k)^{-n}\,(q_0^{-1}-1)]^{-1}$, which tends to zero with $(1-k)^n$. So the total of the fractions of selective deaths is

$$D = k\sum_{n=0}^{\infty} q_n,$$

which is finite. When k is small, taking a generation as a unit of time,

$$\frac{dq}{dt} = -kq\,(1-q),$$

approximately. This is also true if generations overlap. So, approximately,

$$\begin{aligned} D &= k\int_0^{\infty} q\,dt \\ &= \int_0^{q_0} -q\,\frac{dt}{dq}\,dq \\ &= \int_0^{q_0} \frac{dq}{1-q} \\ &= -\ln p_0 + O(k). \end{aligned} \tag{3}$$

If greater accuracy is required, we note that

$$\begin{aligned} \int_{q_{n+1}}^{q_n} \frac{dq}{1-q} &= \ln\left(\frac{1-q_{n+1}}{1-q_n}\right) \\ &= -\ln(1-kq_n) \\ &= kq_n + \tfrac{1}{2}k^2q_n^2 + \tfrac{1}{3}k^3q_n^3 + \ldots. \end{aligned}$$

We require the sum of the first term of this series, namely,

$$D = \sum_{n=0}^{\infty} kq_n.$$

We must subtract suitable terms from the integrand.

$$\begin{aligned} \int_{q_{n+1}}^{q_n} q^r\,dq &= (r+1)^{-1}\,(q_n^{r+1} - q_{n+1}^{r+1}) \\ &= (r+1)^{-1}\,q_n^{r+1}(1-kq_n)^{-r-1}\,[(1-kq_n)^{r+1} - (1-k)^{r+1}] \\ &= kq_n^{r+1}(1-q_n)\,(1-kq_n)^{-r-1}\,[1 - \tfrac{1}{2}kr(1+q_n) + \tfrac{1}{6}k^2r(r-1)\,(1+q_n+q_n^2) + \ldots]. \end{aligned}$$

Hence we find

$$\int_{q_{n+1}}^{q_n} [(1-\tfrac{1}{2}k-\tfrac{1}{12}k^2)\,(1-q)^{-1} + \tfrac{1}{2}k + \tfrac{1}{12}k^2 - \tfrac{1}{6}k^2q]\,dq = kq_n + O(k^4).$$

So
$$D=\int_0^{q_0}[(1-\tfrac{1}{2}k-\tfrac{1}{12}k^2)(1-q)^{-1}+\tfrac{1}{2}k+\tfrac{1}{12}k^2-\tfrac{1}{6}k^2q]\,dq$$
$$=-(1-\tfrac{1}{2}k-\tfrac{1}{12}k^2)\ln(1-q_0)+(\tfrac{1}{2}k+\tfrac{1}{12}k^2)\,q_0-\tfrac{1}{12}k^2q_0^2+O(k^3)$$
$$=(1-\tfrac{1}{2}k-\tfrac{1}{12}k^2)\ln(p_0^{-1})+\tfrac{1}{2}k-(\tfrac{1}{2}k-\tfrac{1}{12}k^2)\,p_0+O(k^3)+O(k^2p_0^2). \quad (4)$$

To obtain the coefficient of k^3 we have only to use the method of undetermined coefficients, adding $k^3[\alpha(1-q)^{-1}+\beta+\gamma q+\delta q^2]$ to the integrand, and equating the coefficient of k^4 to zero.

Clearly if k is small, D is almost independent of k, while if k is large, D is less than $-\ln p_0$. When $k=1$, that is to say, the fitness of **a** is zero, $D=q_0$, for selection is complete after one generation; that is to say, $D=1$, very nearly. If $p_0=10^{-4}$, as suggested, $D=9{\cdot}2$, provided selection is slow. If p_0 were as high as 0·01, or 1 %, D would still be 4·6, while if it were as low as 10^{-6}, D would only be 13·8.

The correction to be made for the fact that q_n does not become zero, but reaches a small value set by the rate of back mutation, is negligible. If the final small value is Q, (3) becomes
$$D=-\ln p_0+\ln(1-Q)$$
$$=-\ln p_0-Q,$$
very nearly. If Q is about 10^{-4} the error is of this order, though, of course, a slight loss of fitness equal to the back mutation rate will go on indefinitely. The same is true for other expressions such as (7).

We may, therefore, take it that when selection is fairly slow, the total number of selective deaths over all generations is usually 5–15 times the total number in the population in each generation, 10 times this number being a representative value. When k exceeds $\frac{1}{3}$, this number is appreciably reduced.

During the course of selection the value of k may vary. If the environment is changing progressively it will, on the whole, increase. But provided it is small this makes no difference to the result. The cost of changing q from q_1 to q_2 is
$$\int_{q_1}^{q_2}\frac{dq}{1-q}+O(k)=\ln\left(\frac{1-q_2}{1-q_1}\right)+O(k),$$
which is nearly independent of the value of k.

Selection at an autosomal locus in a diploid

Consider an autosomal pair of allels **A** and **a** in a large random mating population, with frequencies p_n and q_n in the nth generation. Let their relative fitnesses be as below:

Genotype	**AA**	**Aa**	**aa**
Frequency	p_n^2	$2p_nq_n$	q_n^2
Fitness	1	$1-k$	$1-K$

where $K\geqslant k\geqslant 0$. Let $k=\lambda K$. If $\lambda=1$, **a** is dominant as regards fitness. If $\lambda=0$, $k=0$, and **a** is recessive as regards fitness. λ is usually between 1 and 0. I assume $\lambda\leqslant 1$, for if $k<0$, the gene **A** will not displace **a** completely, but an equilibrium will be reached, while if $k>K$ selection will not occur. For the reasons given above I assume $p_0=5\times10^{-5}$ unless λ is very small or zero, in which case p_0 may be about 0·01.

The fraction of selective deaths in the nth generation is

$$\begin{aligned} d_n &= 2kp_nq_n + Kq_n^2 \\ &= Kq_n[2\lambda + (1-2\lambda)\,q_n]. \end{aligned} \tag{5}$$

So the total deaths are the population number multiplied by

$$D = K\sum_{n=0}^{\infty}[2\lambda q_n + (1-2\lambda)\,q_n^2].$$

Also

$$\begin{aligned} \Delta q_n &= \frac{-p_nq_n[k(p_n-q_n)+Kq_n]}{1-2kp_nq_n-Kq_n^2} \\ &= -Kp_nq_n\,[\lambda+(1-2\lambda)\,q_n], \end{aligned} \tag{6}$$

approximately. Using the same approximation as before,

$$\begin{aligned} D &= \int_0^{q_0}\frac{[2\lambda+(1-2\lambda)\,q]\,dq}{(1-q)\,[\lambda+(1-2\lambda)\,q]} \\ &= \frac{1}{1-\lambda}\int_0^{q_0}\left[\frac{1}{1-q}+\frac{\lambda(1-2\lambda)}{\lambda+(1-2\lambda)\,q}\right]dq \\ &= \frac{1}{1-\lambda}\left[-\ln p_0+\lambda\ln\left(\frac{1-\lambda-p_0}{\lambda}\right)\right] \\ &= \frac{1}{1-\lambda}\left[-\ln p_0+\lambda\ln\left(\frac{1-\lambda}{\lambda}\right)\right], \end{aligned} \tag{7}$$

(provided $\lambda<1$)

nearly. If, however, $\lambda=1$,

$$\begin{aligned} D &= \int_0^{q_0}\frac{(2-q)\,dq}{(1-q)^2} \\ &= \int_0^{q_0}\left[\frac{1}{1-q}+\frac{1}{(1-q)^2}\right]dq \\ &= p_0^{-1}-\ln p_0+O(k). \end{aligned} \tag{8}$$

If $\lambda=0$ (**A** dominant), then from (7), $D=-\ln p_0$, if $\lambda=\frac{1}{2}$, $D=-2\ln p_0$, if $\lambda=\frac{3}{4}$, $D=-4\ln p_0-3{\cdot}3$, and if $\lambda=0{\cdot}9$, $D=-10\ln p_0-19{\cdot}8$. Thus if $p_0=5\times10^{-5}$, $\ln p_0=9{\cdot}9$, and D ranges from 9·9 to about 79. However, when **A** is nearly recessive, p_0 is probably somewhat larger than 5×10^{-5}, and when it is fully recessive p_0 is more probably about 0·01, giving $D=105$ approximately, from (8). Thus D usually lies between 10 and 100, with 30 as a representative value.

We can find corrections to be made when K is not small. They are analogous to (4). In the limiting cases when $K=1$, $k=0$, $D=1$ approximately. While if $K=k=1$,

$$\begin{aligned} D &= 1+\frac{1}{2^2}+\frac{1}{3^2}+\frac{1}{4^2}+\ldots \\ &= \tfrac{1}{6}\pi^2 \\ &= 1{\cdot}645. \end{aligned}$$

Once again the value of D is not affected by the intensity of selection provided this is small, and is not very sensitive to the value of p_0.

Selection at an autosomal locus with inbreeding

If inbreeding is almost complete, as in self-fertilized crop plants, the deaths of heterozygotes can be neglected, and equation (3) holds with sufficient accuracy. If there is partial inbreeding, suppose that gene frequencies and genotypic fitnesses are as in the last section, but the mean coefficient of inbreeding in the population is f instead of zero. Then the survivors of selection occur in the ratios

$$(p_n^2+fp_nq_n)\,\mathbf{AA}:2(1-k)\,(1-f)\,p_nq_n\,\mathbf{Aa}:(1-K)\,(fp_nq_n+q_n^2)\,\mathbf{aa}.$$

Hence
$$d_n=q_n[2k(1-f)\,p_n+K(fp_n+q_n)],$$

$$\Delta q_n=\frac{-p_nq_n[k(1-f)\,(p_n-q_n)+K(fp_n+q_n)]}{1-2k(1-f)\,p_nq_n-K(fp_nq_n+q_n^2)}.$$

Hence
$$D=\int_0^{q_0}\frac{2(1-f)\,k+fK+(1-f)\,(K-2k)\,q}{(1-q)\,[(1-f)\,k+fK+(1-f)\,(K-2k)\,q]}\,dq, \quad \text{nearly}$$

$$=[K-(1-f)\,k]^{-1}\int_0^{q_0}\left[\frac{K}{1-q}+\frac{(1-f)^2\,k(K-2k)}{(1-f)\,k+fK+(1-f)\,(K-2k)\,q}\right]dq$$

$$=[K-(1-f)\,k]^{-1}\left[-K\ln p_0+(1-f)\,k\ln\left(\frac{K-k+fk}{K+fK-fk}\right)\right] \tag{9}$$

nearly. If $(1-f)\,k=\mu K$,

$$D=(1-\mu)^{-1}\left[-\ln p_0+\mu\ln\left(\frac{1-\mu}{\mu}\right)-\ln\left(1+\frac{f}{\mu}\right)\right].$$

That is to say, the effect of partial inbreeding is very nearly to replace λ by $(1-f)\,\lambda$ in equation (7). The value of D is slightly reduced, as if the heterozygotes were a little fitter. But D is never as small as the value given by equation (3). If $k=\frac{1}{2}K$, D is divided by $(1+f)$. Partial inbreeding thus saves a few deaths, but has little effect on the value of D unless **A** is recessive, when it reduces it drastically.

Selection at a sex-linked locus in a diploid

I assume males to be heterogametic. The results are the same, *mutatis mutandis*, if females are so. I assume that selection is so slow that the gene frequencies are very nearly the same in both sexes. Let the frequencies and relative fitnesses be

Genotype	**AA**		**Aa**		**aa**		**A**		**a**
Frequency	p_n^2		$2p_nq_n$		q_n^2		p_n		q_n
Fitness	1	:	$1-k$	:	$1-K$	:	1	:	$1-l$

In fact the frequencies of **a** differ in the two sexes by a quantity of the order of the largest of k, K and l, but this can provisionally be neglected. The selective death-rates in females and males are respectively:

$$\left.\begin{aligned} d_{f,n}&=2kp_nq_n+Kq_n^2,\\ d_{m,n}&=lq_n.\end{aligned}\right\} \tag{10}$$

And
$$\Delta q_n=-\tfrac{1}{3}p_nq_n[2k(p_n-q_n)+Kq_n+l], \tag{11}$$

since there are twice as many loci in female as in male gametes forming the next generation. Thus, the total of female selective death-rates approximates to

$$D_f = 3\int_0^{q_0} \frac{[2k+(K-2k)\,q]\,dq}{(1-q)\,[2k+l+2(K-2k)\,q]}.$$

Provided $2K+l>2k$,

$$D_f = \frac{3}{2K-2k+l}\int_0^{q_0}\left[\frac{K}{1-q}+\frac{(K-2k)\,(2k-l)}{2k+l+2(K-2k)\,q}\right]dq$$
$$= \frac{3}{2K-2k+l}\left[-K\ln p_0+\tfrac{1}{2}(2k-l)\ln\left(\frac{2k+l}{2K-2k+l}\right)\right],$$

and similarly the total for males is

$$D_m = \frac{3l}{2K-2k+l}\left[-\ln p_0+\ln\left(\frac{2k+l}{2K-2k+l}\right)\right]. \tag{12}$$

If, however, $2K+l=2k$, which implies that $k>K$, unless $l=0$, in which case **A** is fully recessive as regards fitness in females,

$$\left.\begin{aligned} D_f &= \frac{3}{2}\left(\frac{K}{K+l}\,p_0-\ln p_0\right),\\ D_m &= \frac{3lp_0}{2(K+l)}. \end{aligned}\right\} \tag{13}$$

It is possible that almost all the selective mortality should be concentrated on the males. This will be so if K is small, provided $2K+l>2k$. This is unlikely but not impossible. For the reasons discussed earlier this would probably not ease the burden on the species very greatly.

The value of p_0 would be about 10^{-4} provided that in the preliminary period **A** males were at an appreciable disadvantage. The mean of D_f and D_m is

$$D = \frac{3}{2(2K-2k+l)}\left[-(K+l)\ln p_0+(k+\tfrac{1}{2}l)\ln\left(\frac{2k+l}{2K-2k+l}\right)\right], \tag{14}$$

unless $2K+l=2k$, when

$$D=\tfrac{3}{2}(p_0-\ln p_0). \tag{15}$$

If $2k>2K+l$ an equilibrium is reached.

We see that the cost of selection at a sex-linked locus depends, as at an autosomal locus, on $-\ln p_0$, and on the ratios of selective intensities, provided these are small. The factor multiplying $-\ln p_0$ will seldom be large. It is, for example, 3 if $K=k=l$, and 1 if $K=l$, $k=0$. Thus a representative value of D is 20, and it will probably be between 10 and 40 in most cases. It will not be greatly increased if the gene selected is completely recessive in females, provided that it is of selective advantage in males.

SELECTION OF HETEROZYGOTES

The total death-rates of heterozygotes at an autosomal locus are given by

$$D_h = \Sigma\, 2kp_nq_n$$
$$= 2\lambda K\Sigma q_n(1-q_n).$$

This approximates to

$$2\lambda K\int_0^{\infty} q(1-q)\,dt = 2\lambda K\int_{q_n}^{q_0} q(1-q)\frac{dt}{dq}\,dq$$

$$= 2\lambda\int_{q_n}^{q_0}\frac{dq}{\lambda+(1-2\lambda)q}$$

$$= \frac{2\lambda}{1-2\lambda}\Big[\ln\{\lambda+(1-2\lambda)q\}\Big]_{q_n}^{q_0}.$$

If $1>\lambda>0$, $$D_h=\frac{2\lambda}{1-2\lambda}\ln\left(\frac{1-\lambda}{\lambda}\right),$$

except when $\lambda=\frac{1}{2}$, when $$D_h=2.$$

If $\lambda=1$, $$D_h=-2\ln p_0. \qquad (16)$$

Over the range considered D_h is a monotone increasing function of λ, being 0·549 when $\lambda=0{\cdot}1$, and 4·944 when $\lambda=0{\cdot}9$. That is to say unless λ is very nearly unity, or **A** almost recessive as regards adaptive value, D_h is small. And it is always a small fraction of D. During most of the course of a gene substitution heterozygotes are rare.

It can easily be shown that in the case of a sex-linked locus the total deaths of heterozygous females are

$$D_h=\frac{3k}{K-2k}\ln\left(\frac{2K-2k+l}{2k+l}\right),$$

unless $K=2k$, when $D_h=3K^2/(K+l)$. These are also relatively small numbers.

In a recent discussion on natural selection (Haldane, 1956*b*) I gave the total numbers of heterozygotes produced in the course of a gene substitution, or $k^{-1}D_h$. The results are equivalent. Since so few heterozygotes are killed, there can, in the course of a gene replacement, be little selection in favour of genes raising the fitness of heterozygotes by altering dominance or otherwise, unless they affect homozygotes also.

Discussion

The unit process of evolution, the substitution of one allel by another, if carried out by natural selection based on juvenile deaths, usually involves a number of deaths equal to about 10 or 20 times the number in a generation, always exceeding this number, and perhaps rarely being 100 times this number. To allow for occasional high values I take 30 as a mean. If natural selection acts by diminished fertility the effect is equivalent.

Suppose then that selection is taking place slowly at a number of loci, the average rate being one gene substitution in each n generations, the fitness of the species concerned will fall below the optimum by a factor of about $30n^{-1}$ so long as this is small. If the depression is larger we reason as follows. If a number of loci are concerned, the ith depressing fitness by a small quantity δ_i, the mean number of loci transformed per generation is $D^{-1}\Sigma\delta_i$ or about $\frac{1}{30}\Sigma\delta_i$. The fitness is reduced to $\Pi(1-\delta_i)$ or about $\exp(-\Sigma\delta_i)$. But $n=30\,\Sigma\delta_i$, roughly. Thus, the fitness is about $e^{-30n^{-1}}$, or the intensity of selection $I=30n^{-1}$.

To be concrete, if a species had immigrated into an environment where its reproductive capacity was half that obtainable after selection had run its course, so that $I=\ln 2=0{\cdot}69$,

n would be 43. This represents, in my opinion, fairly intense selection, of the order of that found in *Biston betularia*, where it has had a rapid effect because it was concentrated on a phenotypic change due mainly to a single gene. I doubt if such high intensities of selection have been common in the course of evolution. I think $n=300$, which would give $I=0{\cdot}1$, is a more probable figure. Whereas, for example, $n=7{\cdot}5$ would reduce the fitness to e^{-4}, or 0·02, which would hardly be compatible with survival.

We do not know at how many loci two 'good' but fairly closely related species differ. Their taxonomic characters may depend mainly on as few as twenty gene substitutions. But there is every reason to think that substitutions have occurred at a great many other loci. Punnett (1932) showed that among eighteen fully recessive mutants in *Lathyrus odoratus* which he studied the viability increased with the time which had elapsed since the mutation occurred. In Table 1 I have presented the data of his Table VI in a different form. The second column is the estimated viability. If d dominants and r

Table 1. *Punnett's data on sweet peas*

	Mutant	Viability	S.E.
g_1	White	1·037	0·024
a_1	Red	1·021	0·017
b_1	Light axil	1·011	0·017
f_1	White	0·996	0·038
d_5	Picotee	0·996	0·022
a_2	Round pollen	0·990	0·024
b_2	Sterile	0·988	0·017
a_3	Hooded	0·977	0·021
e	Cupid	0·976	0·032
f_2	Bush	0·936	0·030
d_2	Blue	0·931	0·024
g_3	Mauve	0·917	0·031
d_1	Acacia	0·964	0·020
d_4	Smooth	0·940	0·020
d_3	Copper	0·909	0·040
h	Spencer	0·897	0·030
b_3	Cretin	0·886	0·048
f_3	Marbled	0·821	0·023

recessives are found out of n, this is $3r/(d+1)$ (Haldane, 1956*c*) and its standard error is $3\sqrt{(rn/d^3)}$. The standard errors are given in the third column. The first group of mutants occurred in wild populations, in the eighteenth, or possibly in the early nineteenth, century. The second group originated between 1880 and 1899. The third group originated between 1901 and 1912. In each group the order is that of viabilities. None of the viabilities in the first group differs significantly from unity, nor does their mean. I know of no equally satisfactory series of data in any other organism. It seems that a mutant on appearance is generally somewhat inviable. But intense selection exercised by breeders accumulates 'modifiers' which, in the course of fifty years or so, raise its viability in F_2 to normal.

Presumably the same kind of process occurs in evolution. The number of loci in a vertebrate species has been estimated at about 40,000. 'Good' species, even when closely related, may differ at several thousand loci, even if the differences at most of them are very slight. But it takes as many deaths, or their equivalents, to replace a gene by one producing a barely distinguishable phenotype as by one producing a very different one. If two species differ at 1000 loci, and the mean rate of gene substitution, as has been suggested, is one

per 300 generations, it will take at least 300,000 generations to generate an interspecific difference. It may take a good deal more, for if an allel a^1 is ultimately replaced by a^{10} the population may pass through stages where the commonest genotype at the locus is a^1a^1, a^2a^2, a^3a^3, and so on, successively, the various allels in turn giving maximal fitness in the existing environment and the residual genotype. Simpson (1953) finds the mean life of a genus of Carnivora to be about 8 million years. That of a species in horotelic vertebrate evolution may average about a million.

Zeuner (1945), after a very full discussion of the Pleistocene fossil record, concluded that in mammals about 500,000 years were required for the evolution of a new species, though in the vole genera *Mimomys* and *Arvicola* the rate was somewhat greater. Some insects seem to have evolved at about the same rate, while other insects, and all molluscs, evolved more slowly. He estimated the total duration of the Pleistocene at 600,000 years, but some later authors would about halve this figure. On the other hand environmental changes during the Pleistocene were unusually rapid, and evolution, therefore, probably also unusually rapid. The agreement with the theory here developed is satisfactory.

Some writers, such as Fisher (1930, 1931), appear to assume that the number of loci at which 'modifiers', for example, genes affecting the dominance of other genes, may be selected, is indefinitely large. The number of loci is, however, finite. But even if enough modifiers were available, the selection of, say, ten modifiers which between them caused a previously dominant mutant to become recessive, would involve the death of a number of individuals equal to about 300 generations of the species concerned. Even the geological time scale is too short for such processes to go on in respect of thousands of loci. Renwick (1956) has made it very probable that dominance modifiers occur at the mutant locus, and if so recessivity may often be assured by strengthening the 'wild-type' allel (Wright, 1934; Haldane, 1939).

Can this slowness be avoided by selecting several genes at a time? I doubt it, for the following reason. Consider clonally reproducing bacteria, in which a number of disadvantageous genes are present, kept in being by mutation, each with frequencies of the order of 10^{-4}. They become slightly advantageous through a change of environment or residual genotype. Among 10^{12} bacteria there might be one which possessed three such mutants. But since the cost of selection is proportional to the negative logarithm of the initial frequency the mean cost of selecting its descendants would be the same as that of selection for the three mutants in series, though the process might be quicker. The same argument applies to mutants linked by an inversion. Once several favourable mutants are so linked the inversion may be quickly selected. But the rarity of inversions containing several rare and favourable mutants will leave the cost unaltered.

There can, of course, be other reasons for the slowness of evolution. In some cases several genes must be substituted simultaneously before fitness is increased. This process can perhaps occur in two ways. On the one hand in a species broken up into small endogamous groups such a combination of genes may be established by a random process of 'drift' (Wright, 1934 and earlier) or a single founder crossing a geographical barrier may possess them (Spurway, 1953). Or they may be linked by an inversion. But such events are not perhaps very frequent even on an evolutionary time scale. On the other hand, each gene may change by a number of small successive steps. Fisher's (1930, pp. 38–40) argument is applicable here, though he may have envisaged changes at a large number of loci, rather than successive changes at a few. In either case the cost is high and the

process must, therefore, be slow. The slowness of evolution of such an organ as the vertebrate eye is thus intelligible.

Evolution by natural selection can be very rapid if a species, like the first land vertebrates, or the first colonists of an island, finds itself in an environment to which it is very ill-adapted, but in which it has no competition, and perhaps no predators and few parasites. If so selection might be so intense as to reduce the capacity for increase to one-tenth of that of its adapted descendants, and it could yet hold its own. Such episodes have doubtless been important, and account for tachytelic (Simpson, 1953) evolution. But they are probably exceptional.

On the whole it seems that the rate of evolution is set by the number of loci in a genome, and the number of stages through which they can mutate. If pre-Cambrian organisms had much fewer loci than their descendants, they may have evolved much quicker, though the possibilities open to them were more limited.

The calculations regarding heterozygotes enable us to answer certain questions. Kettlewell (1956*b*) has evidence that **C** in *Biston betularia* is now more dominant than it was in the nineteenth century. **CC** is now usually indistinguishable from **Cc** by human beings, and probably by birds. This is thought to be due to selection of one or more genes which modify dominance. The value of λ in equations (5) to (8) has decreased from about $\frac{1}{2}$ to nearly zero. If λ was originally $\frac{1}{2}$, the total number of **Cc** moths killed selectively was about twice the number in a generation, and since λ diminished, it can hardly be as many as this.

Now supposing a modifier **M** which made **Cc** as dark as **CC** had been selected by deaths of heterozygotes which did not carry it, the natural logarithm of its frequency would have increased by about 4, from equation (7). That is to say its frequency would have increased about e^4, or 55 times. This is certainly an overestimate, since fewer heterozygotes would have been killed as soon as the modifier became at all common. Probably a twenty-fold increase is the most that could be expected. This is not enough to make **C** almost always dominant when it was previously semi-dominant.

However, two other possibilities are open. It is quite possible that at the present time **Cc** has a higher adaptive value than **CC**, and this accounts for the persistence of **cc** in all populations studied. If so the proportion of **Cc** moths may be much higher that it would be if **CC** had a higher adaptive value than **Cc**. In fact λ may sometimes at least be negative in equation (5), leading to balanced polymorphism. Another possibility is that **M** improves the physiological adjustment of **CC**. Suppose, for example, that **C** is responsible for a tyrosinase or a similar enzyme absent in **cc**, and that **CC** moths produce twice as much of this enzyme as **Cc**. Then if the substrate concentration is low, it may not be possible for **Cc** moths to make enough melanin to become fully black. However, **CC** moths may use up most of the available phenolic substrate, and the resulting shortage may lead to ill-health. There will then be selection for a gene **M** which leads to the synthesis of more substrate, and incidentally permits **Cc** moths to make enough melanin to appear as black as **CC**. This is, of course, only one of many hypotheses. But it is important to realize that a dominance modifier may be selected for its effect on homozygotes.

To conclude, I am quite aware that my conclusions will probably need drastic revision. But I am convinced that quantitative arguments of the kind here put forward should play a part in all future discussions of evolution.

SUMMARY

Unless selection is very intense, the number of deaths needed to secure the substitution, by natural selection, of one gene for another at a locus, is independent of the intensity of selection. It is often about 30 times the number of organisms in a generation. It is suggested that, in horotelic evolution, the mean time taken for each gene substitution is about 300 generations. This accords with the observed slowness of evolution.

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