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The rate of selection advance for non-additive loci

By W. G. HILL
Institute of Animal Genetics, West Mains Road, Edinburgh, 9

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1. INTRODUCTION

Some selection experiments and breeding programmes are continued for many generations until a limit is reached after which no further progress can be made. The breeder may wish to predict before undertaking the programme how long it will take to reach the limit, or at least get a large part of the way there if the approach is asymptotic. The initial rate of advance can usually be predicted adequately using classical quantitative genetics theory from the heritability and selection differential, but when selection is continued for several generations in finite populations the genetic variance and, consequently, heritability change as the gene frequencies alter with drift and selection. The manner in which these change and thus the rate of advance over many generations of selection depend on the effects, frequency and number of genes influencing the quantitative trait. The breeder and experimentalist may therefore be interested in analysing their results in the hope of obtaining some information about the inheritance of the selected trait.

As a measure of the rate of advance Robertson (1960) defined the half-life of the selection process as the time taken to get half-way to the limit. Robertson (1960) and Hill & Robertson (1966) have given results for the half-lives of single additive genes, and Latter (1966) and Hill & Robertson (1966) have discussed some of the effects of linkage on half-lives with pairs of linked additive loci. The half-life can be measured from practical experiments which are taken to the selection limit, and has the advantage in that it is a statistic whose units are solely generations (or years) and do not involve scale factors such as gallons of milk. Also, if the rate of advance is close to exponential in form the half-life and the total advance completely describe the process. This can occur with additive genes with weak selection (Robertson, 1960) or with dominant genes with no selection, when the decline in the mean is proportional to the inbreeding coefficient.

In this paper the influence of initial gene frequency and size of gene effects will be investigated for genes showing complete dominance. The model used will be limited strictly to single loci, but may be expected to hold approximately for many independent loci with the same initial frequency and effect. Of course this cannot represent the real situation for any quantitative trait, but the results should still be of some diagnostic value. The methods used here for calculating the selection advance in finite populations are only approximate, but they have been shown in

the previous paper by Hill (1969) to give a good fit to exact results calculated for a simple model of population structure.

2. MODEL AND METHOD

Consider a single locus with two alleles, at which the favourable allele A has initial frequency q_0. From the original population a large number of replicated finite subpopulations or lines are drawn, and in each selection is practised. The average frequency of A at generation t is $E(q_0)$ and we let $u(q_0) = \lim_{t\to\infty} E(q_t)$. Thus $u(q_0)$ is the chance of fixation of A, and is the probability that at the selection limit it is fixed in the population. The total gain is $u(q_0) - q_0$ and the half-life is the value of t such that

$$E(q_t) - q_0 = \tfrac{1}{2}[u(q_0) - q_0].$$

Hill (1969) has described the model which we shall approximate. Each generation N out of a total of M monecious individuals are selected on their own value for the quantitative trait. These N individuals mate at random, and random selfing is included. If A is dominant over the alternative allele a the expected change in gene frequency in a line with frequency q is approximately $k\alpha q(1-q)^2$. This formula was originally derived by Kojima (1961); k is the mean of the top N from M order statistics from a standardized normal distribution and α is the difference in genotypic value between AA and aa individuals expressed as a proportion of the standard deviation of phenotypic values about the genotypic value. If A is the only locus affecting the trait α remains constant, and we let $s = k\alpha$. Hill (1969) has shown that a transition probability matrix $\mathbf{B}$ with elements (b_{ij}), $i, j = 0, \ldots, 2N$ given by

$$b_{ij} = \binom{2N}{j}\left[\frac{i}{2N} + s\frac{i}{2N}\left(1 - \frac{i}{2N}\right)^2\right]^j\left[1 - \frac{i}{2N} - s\frac{i}{2N}\left(1 - \frac{i}{2N}\right)^2\right]^{2N-j}$$

is a suitable approximation for the transition probability matrix in which the selection process is described exactly. The element b_{ij} is the (approximate) probability that the N parents contain jA alleles at generation $t+1$ given that they had i at generation t.

Since the matrix $\mathbf{B}$ is easy to compute it has been used for all the results given in this paper. A large value of $N(32)$ has been used, such that k is close in value to i, where

$$i = \lim_{N\to\infty} k,$$

with N/M constant. Thus the selective value of the gene is approximately $i\alpha$ which appears in the well-known formulae for selection in infinitely large populations (e.g. Griffing, 1960). Using a diffusion equation to give a continuous approximation to the selection process it can be shown that the selection limit is a function of only Ns and q_0, and that the mean gene frequency at generation t is a function of the same parameters and also t/N. This simplifying assumption has also been investigated by Hill (1969) and found to be an adequate approximation for most descriptive purposes.

Since we are concerned now with the genetic implication of the results one change in definition will be made compared with the previous paper (Hill, 1969). Selective values will always be assumed to be positive; the allele favoured by selection will have initial frequency q_0 and it will be stated whether this allele is recessive or dominant over its alternative.

In the limiting case as Ns becomes very small an explicit formula for the average gene frequency has been given by Robertson (1960). With the recessive allele favoured

$$E(q_t) = q_0 + Nsq_0(1-q_0)[1-e^{-t/2N} - \tfrac{1}{3}(1-2q_0)(1-e^{-3t/2N})]$$

approximately. This formula was used to compute the half-life of the gene frequency for the limiting value as Ns becomes zero by solving for t with the mean frequency half-way to its limiting value. For larger values of Ns the transition matrix **B** was iterated repeatedly onto a vector of mean gene frequencies. The method is described in detail by Hill (1969).

3. CHANGES IN GENE FREQUENCY

Half-lives for the change in gene frequency are given for a wide range of parameters in Figs. 1–3. Figure 1 shows the case of additive gene action which has been included for comparison and is reproduced from Hill & Robertson (1966). In the additive model the two homozygotes differ in selective value by $s = k\alpha$. The transition matrix used was analogous to the approximate matrix **B** for complete dominance. Rows of the matrix were obtained by a binomial expansion with index $2N$ and mean $(i/2N) + s(i/2N)[1-(i/2N)]$. The allele favoured by selection is a recessive in Fig. 2 and a dominant in Fig. 3.

Further information on the pattern of responses is contained in Table 1. There the ratio of quarter-lives to half-lives $t(\frac{1}{4})/t(\frac{1}{2})$ and the ratio of half-lives to three-quarter lives $t(\frac{1}{2})/t(\frac{3}{4})$ are given for a few values of the parameters Ns, q_0 and mode of gene action. The quarter-life is, of course, the time taken to qet a quarter of the way to the limit. If the pattern of advance is exponential, of the form

$$E(q_t) - q_0 = [u(q_0) - q_0](1-e^{-u})$$

then $t(\frac{1}{4})/t(\frac{1}{2}) = 0{\cdot}415$ and $t(\frac{1}{2})/t(\frac{3}{4}) = 0{\cdot}500$, independent of the value of the constant l. With additivity, as $Ns \to 0$ changes are approximately exponential and $l = 1/2N$ (Robertson, 1960). Small values of $t(\frac{1}{4})/t(\frac{1}{2})$ and $t(\frac{1}{2})/t(\frac{3}{4})$ reflect rapid early advance followed by a prolonged period of relatively slower advance.

With small Ns the half-life of a favourable recessive gene is $2{\cdot}1N$ if q_0 is close to zero, and is $1{\cdot}0N$ if q_0 is close to unity, with intermediate values being obtained for other initial frequencies. When $q_0 = 0{\cdot}5$, the half-life is $1{\cdot}4N$, which is the same as for additive genes with all values of q_0 and small Ns (Robertson, 1960). When the recessive is favoured an increase in Ns always reduces the half-life for any starting frequency, reflecting the fact that for a given value of N the larger Ns then the greater the selective value s and the rate of advance. Similarly, for any specific value of Ns the half-life is always less with higher initial frequency apparently because the favoured allele requires a smaller change in frequency before fixation.

A similar result is obtained for additive genes although the effect is not so pronounced. With recessive genes, when the response is proportional to $sq^2(1-q)$, slow rates of advance are clearly made if the frequency is low.

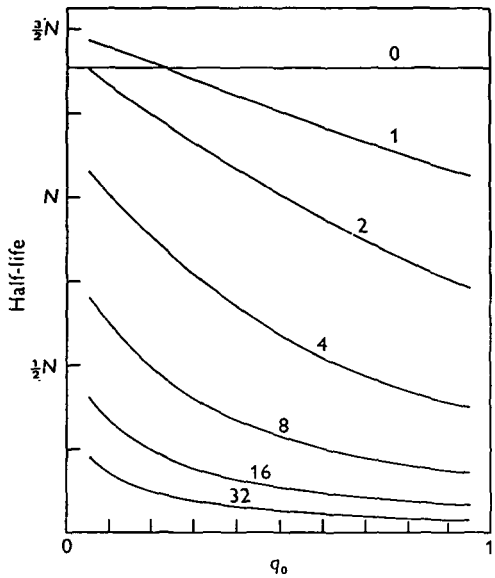

Fig. 1

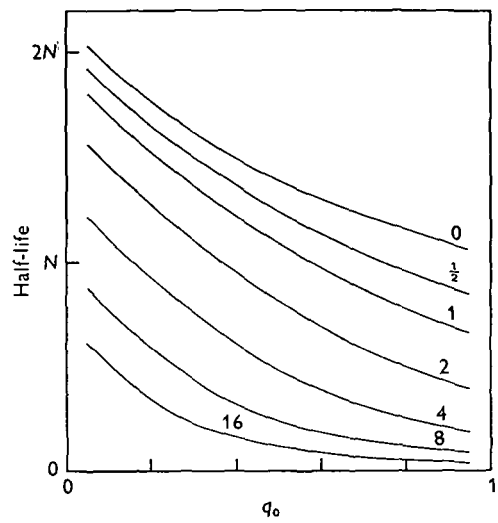

Fig. 2

Fig. 1. Half-life of change in gene frequency with selection for an additive gene. Time is measured in generations, and curves are plotted for different values of Ns with initial frequency q_0. (Reproduced from Hill & Robertson, 1966.)

Fig. 2. As Fig. 1, but with selection for a favourable recessive gene.

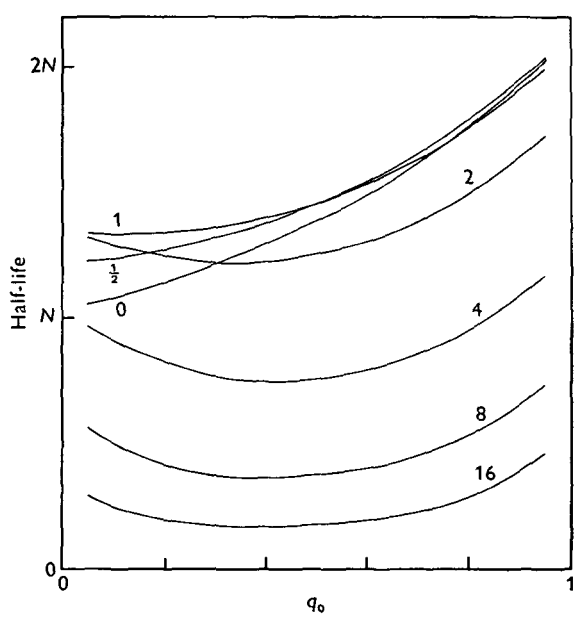

Fig. 3. As Fig. 1, but with selection for a favourable dominant gene.

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However, when the dominant allele is favoured we see in Fig. 3 that unless Ns is small the shortest half-lives occur with intermediate initial frequencies, the minima in the curve occurring at about $q_0 = 0{\cdot}4$. It would seem that two counteracting forces cause this minimum. With high initial frequencies the half-life is long, because the rate of advance, proportional to $sq(1-q)^2$ is low at a high frequency of the dominant. On the other hand, with low initial gene frequency the half-life is prolonged because a greater total advance is required before the desired allele is fixed. The latter effect becomes less important with very small Ns values and low q_0 for the favourable allele is rarely fixed, so that there is no minimum in the curve of half-life against q_0 for small Ns when the favourable allele is dominant.

Table 1. *Ratio of quarter-life to half-life* $t(\frac{1}{4})/t(\frac{1}{2})$ *and half-life to three-quarter-life* $t(\frac{1}{2})/t(\frac{3}{4})$ *measured for* $E(q)$ *for various sets of parameters*

	$t(\frac{1}{4})/t(\frac{1}{2})$			$t(\frac{1}{2})/t(\frac{3}{4})$		
Initial frequency (q_0)...	0·1	0·5	0·9	0·1	0·5	0·9
			Additive model			
Ns 0	0·415	0·415	0·415	0·500	0·500	0·500
1	0·442	0·416	0·395	0·528	0·502	0·477
4	0·513	0·436	0·402	0·599	0·521	0·480
16	0·589	0·463	0·419	0·674	0·565	0·506
			Recessive model			
Ns 0	0·512	0·415	0·390	0·571	0·500	0·462
1	0·539	0·428	0·386	0·599	0·510	0·453
4	0 592	0·467	0·406	0·654	0·548	0·487
16	0·659	0·514	0·450	0·697	0·628	0·529
			Dominant model			
Ns 0	0·390	0·415	0·512	0·462	0·500	0·571
1	0·409	0·405	0·495	0·482	0·492	0·555
4	0·471	0·391	0·483	0·529	0·472	0·548
16	0·534	0·386	0·449	0·559	0·424	0·526

When we compare the half-lives for the change in gene frequency for the three models in Figs. 1–3 we find that at intermediate initial frequencies the half-lives are about the same in each case, and for $Ns \to 0$ and $q_0 = 0{\cdot}5$ they become exactly the same. If the desired allele has a low initial frequency the half-life is shortest if it is dominant and longest if it is recessive. By contrast, if the favoured allele has a high initial frequency the ranking is reversed.

4. CHANGES IN THE POPULATION MEAN OF THE QUANTITATIVE TRAIT

We are not usually able to observe changes in gene frequency for dominant genes in single lines, although we can observe changes in the mean of the quantitative trait under selection. However, if crosses are made between replicated lines the response in the mean of the metric trait in crossbred inidividuals will be proportional to the response in gene frequency. With additive genes the pattern of

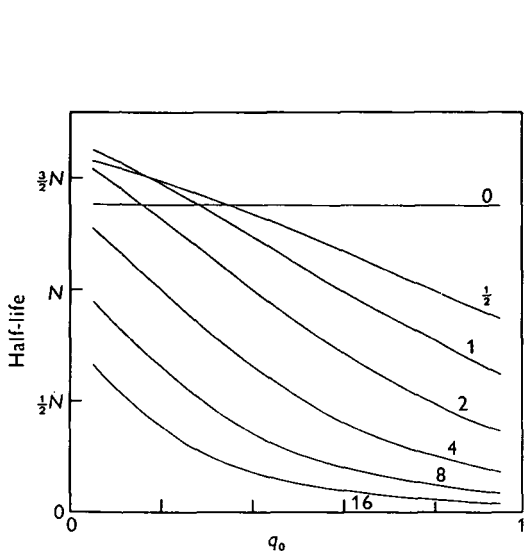

Fig. 4

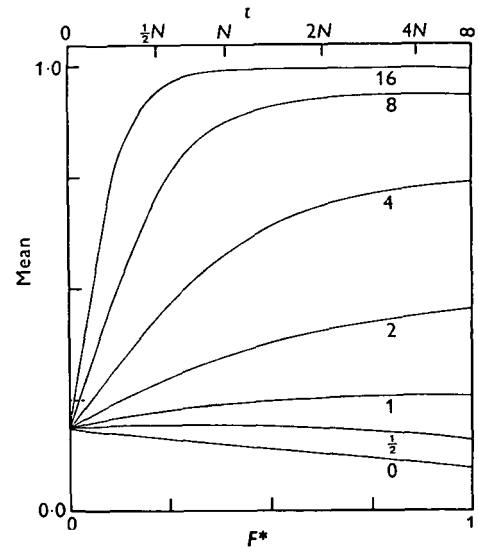

Fig. 5

Fig. 4. Half-life of change in the population mean with selection for a favourable recessive gene. Time is measured in generations and curves are plotted for different values of Ns with initial frequecy q_0.

Fig. 5. The population mean, expressed as the average value of $1-(1-q)^2$, for selection for a favourable dominant gene with initial frequency 0·1. Time is shown in terms of $F^* = 1-\exp(-t/2N)$ (lower scale) and in generations (upper scale). The response is plotted for several values of Ns.

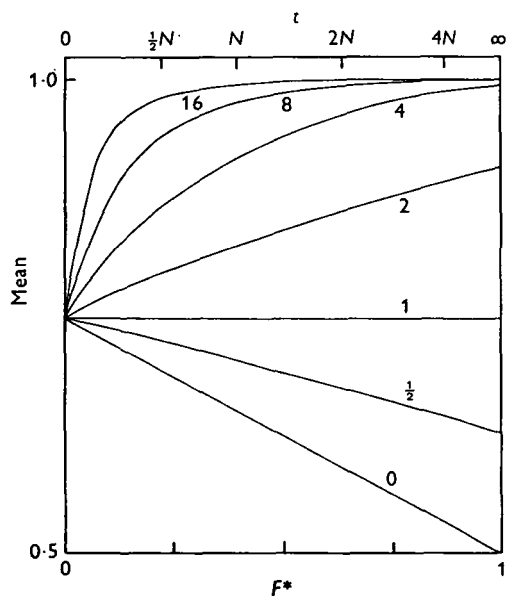

Fig. 6

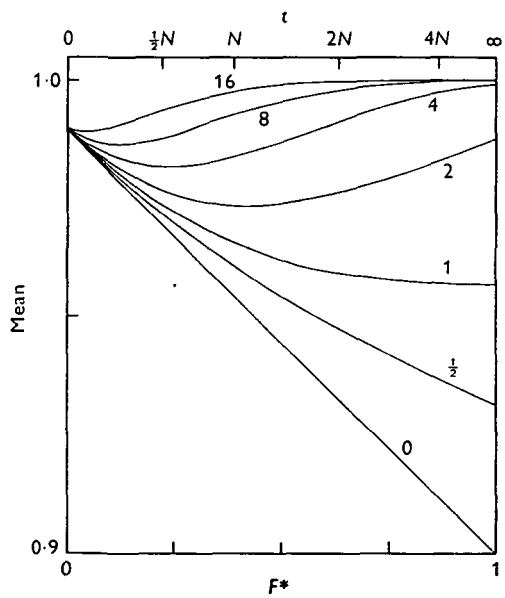

Fig. 7

Fig. 6. As Fig. 5, but with initial frequency 0·5.

Fig. 7. As Fig. 5, but with initial frequency 0·9.

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change in the population mean (for the quantitative character) is the same as for the gene frequency, even in a single line, since the mean is a linear function of gene frequency. However the mean of the trait is proportional to q^2 with a recessive, or $[1-(1-q)^2]$ with a dominant gene in a single population. We therefore need to determine the pattern of change in this mean also. Thus the expected value of q^2_t at each successive generation was computed using the matrix **B** in the same manner as $E(q_t)$ had been computed (Hill, 1969). A half-life for the population mean was also calculated.

The population mean is affected both by selection and by inbreeding depression unless there is additivity, and these effects oppose each other when the dominant allele is favoured. As a result, changes in the mean may be in a direction opposite to that in which selection is practised, or the direction of the response may alter after a few generations of selection, and the half-life is then not a very useful concept. Therefore, while half-lives are shown in Fig. 4 for the population mean of favourable recessives, where inbreeding enhances the advance, some response curves are presented for the case of favourable dominants. In Figs. 5–7 for initial frequencies of 0·1, 0·5 and 0·9 respectively, the expected value of the quantitative trait is plotted against generation number. The scale of generations is transformed to $F^* = 1-e^{-t/2N}$, which is approximately equal to $1-(1-1/2N)^t$, the inbreeding coefficient for neutral genes, and generally provides a suitable contraction of the time scale as t becomes large.

If there is no selection, so that $Ns = 0$, the only force is inbreeding depression and the half-life is reached when $F^* = 0{\cdot}5$, which takes $1{\cdot}4N$ generations for all initial frequencies. At higher Ns values the pattern of half-lives is much the same for both mean and gene frequency when there is selection for the recessive allele. The half-life of the mean for the case of the desirable recessive only exceeds $1{\cdot}4N$ generations when the initial frequency is low and Ns takes intermediate values. Selection then increases the probability of fixation of the favourable allele but requires a long period of selection before fixation because there is a slow initial response with a low-frequency recessive. With higher Ns values fixation of the favourable allele can occur more rapidly.

Selection for a dominant allele is able to counteract the effects of inbreeding sufficiently so that the final mean exceeds the initial mean if Ns is greater than about 0·5 for $q_0 = 0{\cdot}1$, or about 1 for $q_0 = 0{\cdot}5$ and 2 for $q_0 = 0{\cdot}9$. However, at low initial frequencies there may be a period of an advance in the mean, followed by a slight decline, whereas at higher frequencies the decline occurs in the earlier generation. These results reflect the low rate of response obtained with favourable dominants at high initial frequency. In the first few generations there is little additive variance (proportional to $q(1-q)^3$), but this increases as random drift moves the frequency in some replicates to intermediate values (Robertson, 1952; Hill & Robertson, 1968).

5. DISCUSSION

In the model studied we have assumed that only a single locus influences the quantitative trait. However, the results can be expected to hold approximately for several independent loci so long as the selective values of the genes do not change too much as a result of selection. With a heritability of 0·25, for example, the value of the phenotypic standard deviation could decrease by about 10% if all genes went to fixation. Since α is inversely proportional to the phenotypic standard deviation it would correspondingly increase by about 10%. But we see in the graphs that this magnitude of change in α and hence Ns has little qualitative effect on the results. These assumptions have been discussed further by Hill (1969).

The pattern of response we have found is greatly affected by the nature of the gene action. Generally a short half-life, say $N/2$ or less generations, indicates that the gene has a high selective value. Thus if artificial selection is being practised for a quantitative trait which is likely to be affected by several loci, a short half-life may indicate that at least some of the genes have a large effect on the selected trait. However earlier work has shown that the half-lives of additive genes which are initially in linkage equilibrium are usually reduced if they are tightly linked to other genes undergoing selection (Latter, 1966; Hill & Robertson, 1966).

These results have been used in practice to analyse results from selection experiments. Roberts (1966) has calculated the half-life from selection studies on body weight in mice which had been continued till a plateau was reached. From the half-life Roberts estimated the average size of gene effects and the number of loci influencing the selected trait. But with this technique it is necessary to make very strong assumptions about the distribution of initial gene frequencies and effects, usually that they are the same for all loci. If it is also assumed that the loci are independent, when, in fact, some may be closely linked, estimates of gene effects are likely to be biased upwards.

SUMMARY

Expected changes in the gene frequency and the population mean for a quantitative trait are described for selection in a population of size N at a single locus where the favoured allele has initial frequency q_0 and selective value s. Models of additive and completely dominant gene action are compared. Results are generally expressed as the half-life of the total change relative to N.

If the favoured allele is additive or recessive the half-life of the gene frequency and mean of the trait are usually reduced when q_0 or Ns is increased. However, if the dominant allele is favoured the half-life of gene frequency is still generally reduced as Ns is increased, but has a minimum at low or intermediate values of q_0. Since inbreeding depression and selection oppose each other when the dominant allele is favoured the response in the mean of the quantitative trait may change in direction during selection.

REFERENCES

GRIFFING, B. (1960). Theoretical consequences of truncation selection based on the individual phenotype. *Aust. J. biol. Sci.* **13**, 307–343.

HILL, W. G. (1969). On the theory of artificial selection in finite populations. *Genet. Res.* **13**, 143–163.

HILL, W. G. & ROBERTSON, A. (1966). The effect of linkage on limits to artificial selection. *Genet. Res.* **8**, 269–294.

HILL, W. G. & ROBERTSON, A. (1968). The effects of inbreeding at loci with heterozygote advantage. *Genetics* **60**, (in Press).

KOJIMA, K. (1961). Effects of dominance and size of population on response to mass selection. *Genet. Res.* **2**, 177–188.

LATTER, B. D. H. (1966). The response to artificial selection due to autosomal genes of large effect. III. The effects of linkage on the rate of advance and approach to fixation in finite populations. *Aust. J. biol. Sci.* **19**, 131–146.

ROBERTS, R. C. (1966). The limits to artificial selection for body weight in the mouse. I. The limits attained in earlier experiments. *Genet. Res.* **8**, 347–360.

ROBERTSON, A. (1952). The effect of inbreeding on the variation due to recessive genes. *Genetics* **37**, 189–207.

ROBERTSON, A. (1960). A theory of limits in artificial selection. *Proc. R. Soc.* B **153**, 234–249.