THE SELECTIVE COEFFICIENTS THAT KEEP MODIFYING GENES IN A POPULATION

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A gene's effects on fitness can be determined only if it produces a distinct phenotype of a known polymorphism. It is then possible to measure the phenotype's chances of survival against other phenotypes, as, for example, did CLARKE and SHEPPARD (1966) for the melanic and non-melanic forms of the moth *Biston betularia*. But if a character can take any value in a continuous range, there is often complete ignorance of how many genes are causing the variation, of how they are organized into chromosomes, of what pleiotropic effects they may have on other characters and of what their fitnesses may be. The character may be some easily measured part of an organism, like the length of a particular organ. Or it may be the degree of expression of a particular genotype in a polymorphism. For example, the degree of dominance of two alleles is determined by genetic variations in the expression of their heterozygote. The genes that produce quantitative variation of this sort may be called polygenes or modifying genes or modifiers. A particular allele at a particular locus modifies the phenotype by a particular amount on the average. In general the modifiers may interact with each other so that the effect of one modifier may vary according to the other modifiers in the genotype.

To understand how selection may change a character, it is necessary to know how the modifiers are held in the population. Do the modifiers of one character also modify other characters? If so, do their effects on the several characters cause variations in fitness? And how large are the selective coefficients? KIMURA (1968) has shown that one nucleotide must have been substituted for another in the genotype every two years on average during the evolution of the mammals. This rate of replacement implies that many of the mutations can have no effect on fitness; for if they did, the genetic load would be intolerable. This means either that many mutations are simply without any phenotypic effect and make no contribution to the variance of any character, or that a lot of the variation has no effect on fitness.

Suppose the modifiers do have a considerable pleiotropic effect on fitness. The simplest way of maintaining the modifiers in the population is by a superiority of the heterozygotes over the homozygotes. Frequency-dependent selection could also maintain them. YARBOROUGH and KOJIMA (1967) have shown that frequency-dependent selection maintains the polymorphism at the esterase-6 locus in *Drosophila melanogaster*. If selection is then applied to the modifiers in one

direction or the other, it will be opposed by the heterozygous advantage or frequency-dependent selection that maintains the modifiers in the population through their pleiotropic effects. If only weak selection is applied, it will presumably have but little effect against the pleiotropic selective forces. This argument has been used to question the validity of FISHER's (1928) theory of the evolution of dominance: EWENS (1967) has shown that the selective forces acting on the modifiers of a rare deleterious mutant heterozygote are always extremely small. Thus if the modifiers are also being kept in the population by pleiotropic selective forces of a much greater magnitude, they cannot then be selected to improve the fitness of the mutant heterozygote. The wild type will not, therefore, evolve dominance as FISHER thought. But if a rare allele can be shown to have evolved dominance, then it should be possible to calculate the largest possible pleiotropic heterozygous advantage that could maintain a modifier in the population and at the same time be small enough to allow dominance to evolve. If the heterozygous advantage were too great, the modifier would be maintained at an equilibrium too stable to shifted by the weak selective forces of dominance modification.

Among the many different mimetic forms of the butterfly *Papilio dardanus*, there are some rare dominant mimics. Their dominance appears to be determined by modifiers (CLARKE and SHEPPARD 1963). The object of this paper is to show by computer simulation what heterozygous advantages could initially be maintaining the modifiers of dominance and also allow a rare mimic to evolve dominance—as the rare mimics of *Papilio dardanus* appear to have done. The model for the evolution of the mimicry was described in detail by SHEPPARD (1962). It is an elaboration of FISHER's (1930) original model of the evolution of mimicry: modifiers are selected to improve the mimicry of a new mutation producing initially a poor or imperfect mimic.

Rare dominant mimics of Papilio dardanus: CLARKE and SHEPPARD (1960a; b) showed that the mimetic polymorphism of *Papilio dardanus* is controlled by a complicated series of alleles, each allele showing complete dominance or recessiveness to each of the other alleles. The dominance breaks down in F_1 hybrids when the mimics are crossed with the isolated non-mimetic race *meriones*. In crosses between different isolated races of mimics, the mimetic patterns are also disrupted and very poor mimics showing a wide range of characters are produced. These results can be understood if the different mimics and their dominance relations have evolved by the selection of different modifiers in the different races. Each race will be assumed to be more or less homozygous for particular modifiers producing complete dominance and good mimicry of each mimic. The F_1 hybrids between the races will, therefore, be heterozygous for the modifiers; and, as long as the modifiers are not themselves dominant, the dominance and mimicry will break down. Since the hybrids are generally intermediate between their parents, the modifiers' heterozygotes apparently produce phenotypes distinct from those of the races in the hybrid. The modifiers must therefore be homozygous to produce their modifying effects. This is also shown by the backcrosses and intercrosses which CLARKE and SHEPPARD (1963) made. In one of the series of experiments, the mimic *hippocoonides* was crossed with the yellow non-mimetic race *meriones*

to produce the F_1 hybrid yellow/*hippocoonides*. This hybrid was then backcrossed to the mimic *cenea* from the same stock as *hippocoonides*. The offspring from the two broods were: 18 more or less like *cenea*, 10 yellow/*hippocoonides*, 6 yellow/*cenea* and 9 *hippocoonides*. If H^yH^y is the genotype of *meriones* and hh the genotype of *hippocoonides*, then the backcross was $H^yh \times H^ch$, where H^c is the *cenea* allele dominant to h. If M is a modifier making H^c dominant to h when M is homozygous, then the backcross was $Mm\ H^yh \times MM\ H^ch$, where m is the allele corresponding to M in the race *meriones*. The 18 offspring like *cenea*, therefore, had the genotype $MM\ H^ch$ or $Mm\ H^ch$: some of them should be more or less typical *cenea* (the $MM\ H^ch$ individuals) and the others (the $Mm\ H^ch$ individuals) should have undergone a breakdown of their mimicry. According to CLARKE and SHEPPARD, all the *cenea*/*hippocoonides* individuals showed some disruption of the mimetic pattern of *cenea*, but some were very different from the typical *cenea* being more like one of the other mimics. These results are therefore more or less as expected, but since some disruption of mimicry occurs in all heterozygotes, more than one modifying locus must be involved.

The rate of the evolution of dominance depends on the frequency in the population of the heterozygotes to be modified: if there are many of them they can be modified quickly. It is obvious that if the entire population were heterozygous, then a modifier of the heterozygote would be selected at the same rate as any gene having a direct selective effect: the smaller the proportion of heterozygotes in the population, the less direct the selection of the modifier. FORD (1936) quotes unpublished data of a random sample of *Papilio dardanus* from East Africa in which some of the mimics are quite rare. The sample consisted of the mimics:

hippocoon	70	(60%)
(a variation of *hippocoonides*)		
planemoides	21	(18%)
swynnertoni	4	(3.5%)
cenea	8	(7%)
niobe	8	(7%)
trophonissa	5	(4.5%)
(a variation of *trophonius*)		

He also quotes the following data from POULTON (1929) of a sample from South Africa:

cenea	129	(85%)
hippocoonides	14	(9%)
trophonius	6	(4%)
leighi (a non-mimic)	3	(2%)

CLARKE and SHEPPARD (1960c; 1962) showed that most of these mimics are completely dominant or recessive to each other. Thus *trophonius* is dominant to *hippocoonides* and *cenea*; *leighi* is dominant to the others except for the *leighi*/*trophonius* heterozygote which is distinct from both *leighi* and *trophonius*. Such heterozygotes are of course extremely rare in nature. Presumably at such very

low frequencies, the selection of the modifiers of dominance is still going on very slowly or has been stopped by the pleiotropic selective forces of the modifiers opposing the evolution of dominance. But the *trophonius* mimic has evolved complete dominance over the abundant *cenea* mimic and so has *leighi*. Thus if a pleiotropic heterozygous advantage keeps a modifier at a stable equilibrium, it must be small enough to allow a mimic at a frequency of 2–4% to evolve dominance.

SHEPPARD (1962) put forward a model of the evolution of dominance in a mimetic polymorphism. When a new mimic arises by mutation it is unlikely to resemble a distasteful or harmful model very closely. But it must occasionally be mistaken for the model by a predator or it would never start to spread through the population. As it spreads, modifiers improving its resemblance to the model will also be selected for. Heterozygotes of the new mimic will appear first: homozygotes will be very rare until the mimic has become quite common. Thus first the heterozygote and then the homozygote will have their resemblance to the model improved. Since both heterozygote and homozygote come to resemble the same model, the new mimic becomes dominant. Such mimetic polymorphisms are maintained by frequency-dependent selection which produces a stable equilibrium of the mimics (CLARKE and O'DONALD 1964). CLARKE (1964) called the equilibrium frequencies the focal frequencies. They are the frequencies at which the phenotypes have no selective advantage over each other. Obviously the mimic of a very distasteful or harmful model can become more common than the mimic of an only slightly distasteful model before its selective advantage is lost. The mimic of a common model can also become more common than the mimic of a rare model. The palatabilities and frequencies of the models determine the focal frequencies of their mimics.

To construct a model of the evolution of dominance of the rare mimics of *Papilio dardanus* it must be assumed that their frequencies of 2 and 4% are focal frequencies at which the mimic has reached equilibrium with no frequency-dependent selective advantage. If M is a modifier, then the simplest model suggested by CLARKE and SHEPPARD's results is that MM produces complete dominance of one mimic, mm produces complete dominance of the other mimic and Mm produces a form distinct from both mimics. Thus, suppose there are the following frequencies of the nine genotypes:

	AA	Aa	aa
MM	r	u	x
Mm	s	v	y
mm	t	w	z

There are three phenotypes: a mimic of the form A, a mimic of the form a and a distinct heterozygote of genotype $AaMm$. They have the following genotypes, focal frequencies and selective coefficients.

genotypes: $AA\ MM$ $AAMm$ $Aa\ Mm$ $aa\ MM$ $aa\ Mm$
                $AA\ mm$ $AaMM$ $aa\ mm$ $Aa\ mm$

phenotypes:	mimic A	distinct	mimic a
		heterozygotes	
focal frequencies:	F_1	F_2	F_3
selective			
coeefficients:	$s_1=K(r+s+t+u-F_1)$	$s_2=K(v-F_2)$	$s_3=K(x+y+z+w-F_3)$

K is the constant of frequency-dependent selection. It determines the intensity of the selection. The values of s_1, s_2 and s_3 are the frequency-dependent selective coefficients: s_1 is the selective coefficient of the genotypes $AA\ MM$, $AA\ Mm$, $AA\ mm$ and $Aa\ MM$; s_2 is the selective coefficient of the genotype $Aa\ Mm$; and s_3 is the selective coefficient of the genotypes $Aa\ mm$, $aa\ MM$, $aa\ Mm$ and $aa\ mm$.

The modifiers are also subject to an heterozygous advantage independent of their modifying effects on the frequency-dependent selective coefficients. This heterozygous advantage acts before the mimics are subjected to the frequency-dependent selection. The genotypes MM, Mm and mm are given selective coefficients c, 0 and d, to produce a superiority of the heterozygotes. Therefore, before selection of the mimics begins, the modifier M is maintained in the population at an equilibrium frequency of $d/(d+c)$. In the calculations with this model, the modifier was given initial frequencies of either 0.5 or 0.1 at an equilibrium determined by the heterozygous advantage. Thus if the initial frequency was 0.5, then $d=c$, and d measures the heterozygous advantage. (See O'DONALD 1968 for the details of the computer model.) The frequencies of the nine genotypes were computed for each generation by recurrence equations for selection at two loci. The computation was stopped when the change of gene frequency was less than 0.00001. Thus, the frequency of the rare mimic and its modifier was obtained throughout the evolution to equilibrium.

Results of computer simulations: Table 1 shows the frequencies of the modifier of a mimic which arises by mutation and increases in the population to a focal frequency of 4%—the frequency of the *trophonius* mimic of *Papilio dardanus* in South Africa. Because its focal frequency is low, the values of K represent very weak selection. If the mimic has just arisen by mutation, the frequencies of AA and Aa are negligible in comparison with their focal frequencies. Thus if $K=0.5$, we have

		distinct	
phenotype:	mimic A	heterozygote	mimic a
focal frequencies:	0.04	0	0.96
initial selective			
coefficients:	−0.02	0	0.02

The new mimic A has only a 2% advantage over a at first and this advantage decreases as its focal frequency is approached. This explains why selection is so slow. If a were increasing from a low initial frequency, however, it would be very advantageous at the start of selection, its selective advantage being just under 50%: at a low frequency a is a long way from its focal frequency and hence at a correspondingly great advantage; whereas A is near its focal frequency when it is rare and hence at no great advantage. From Table 1, it can be seen quite

TABLE 1

Frequencies of a modifier of the dominance of a mimic which has a focal frequency of 4 percent

(i) $K = 0.5$

Number of generations	Pleiotropic heterozygous advantage of modifier					
	0	0.001	0.002	0.003	0.004	0.005
0	.5	.5	.5	.5	.5	.5
100	.50033	.50032	.50032	.50031	.50031	.50030
200	.50244	.50238	.50232	.50227	.50221	.50216
500	.52950	.52730	.52532	.52353	.52192	.52046
1000	.57993	.56581	.55482	.54623	.53946	.53408
2000	.68015	.62191	.58573	.56333	.54903	.53951
5000	.86504	.69253	.60561	.56902	.55077	.54006
10000	.94300	.71222	.60707	. . . . .	. . . . .	. . . . .
20000	.97490	.71416	. . . . .	. . . . .	. . . . .	. . . . .

(ii) $K = 0.2$

Number of generations	Pleiotropic heterozygous advantage of modifier					
	0	0.001	0.002	0.003	0.004	0.005
0	.5	.5	.5	.5	.5	.5
100	.50006	.50006	.50006	.50006	.50006	.50006
200	.50020	.50019	.50018	.50018	.50017	.50017
500	.50233	.50219	.50207	.50196	.50185	.50176
1000	.51915	.51679	.51483	.51319	.51182	.51066
2000	.55903	.54137	.53032	.52317	.51839	.51506
5000	.67969	.57309	.53949	.52616	.51945	. . . . .
10000	.82487	.58297	.54005	. . . . .	. . . . .	. . . . .
20000	92515	.58411	. . . . .	. . . . .	. . . . .	. . . . .

clearly that when the heterozygous advantage which is maintaining the modifier at a frequency of 0.5 is greater than 0.001 or 0.1%, there is then very little evolution of dominance. If the heterozygous advantage is 0.001, the modifier reaches a frequency of 0.71416 at equilibrium. This represents a state of semi-dominance with half the heterozygotes resembling the mimic *A*. Table 2 shows the final equilibria of the modifiers when they are subjected to different pleiotropic heterozygous advantages and modify mimics with different focal frequencies. Assuming that a mimic like *Papilio dardanus leighi* has reached its focal frequency, Table 2 shows that it could not have evolved dominance if the modifiers had been maintained by heterozygous advantages of more than about 0.0002–0.0004. In practice several modifying loci must be involved and at each of the loci the modifiers must be at equilibria determined by the balance of the selective forces. Even so the modifiers must reach a high frequency for dominance to become more or less complete. The results of the computing therefore give a very rough idea of the magnitude of the greatest possible heterozygous advantage that might maintain the modifiers in the population. The actual heterozygous advantage could, of course, be much less than this. Indeed it is possible that the modifiers are subject to no other selective forces. Only genetic drift would then stop dominance

TABLE 2

Equilibrium frequencies of the modifier with different focal frequencies of the mimic

Pleiotropic heterozygous advantage	Focal frequency of mimic evolving dominance		
	0.03	0.025	0.02
0	.95142*	.92480*	.87118*
0.0001	.91042	.86894	.79497*
0.0002	.86389	.80923	.72543
0.0003	.81739	.75373	.67174
0.0004	.77405	.70709	.63373
0.0005	.73568	.67047	.60741
0.0006	.70312	.64266	.58891
0.0007	.67630	.62163	.57551
0.0008	.65451	.60554	.56549
0.0009	.63685	.59300	.55776

* The symbol indicates the gene frequency after 20000 generations when equilibrium had not been reached but the computation had been stopped. The other values are true equilibria reached before 20000 generations. In all cases the modifier started at a frequency of 0.5, being kept at that frequency by its pleiotropic heterozygous advantage.

evolving in rare heterozygotes. Very similar results are obtained if the modifier starts at an initial equilibrium frequency of 0.1

The selection keeping the modifiers in equilibrium: Genetic drift might be expected to have an effect even though the heterozygotes being modified are not very rare. The heterozygote *cenea/leighi* is at a frequency of just under 2% and it has been shown that the modifiers could not be subjected to an heterozygous advantage of more than about 0.0004. This is a very small selective force and it could be argued that genetic drift would eliminate the modifiers. But suppose it is not an heterozygous advantage but frequency-dependent selection that maintains the modifiers. In general frequency-dependent selection can be intense when frequencies are a long way from equilibrium but weak when they are near equilibrium. Thus an equilibrium maintained by frequency-dependent selection may be no more stable than one maintained by an heterozygous advantage but genetic drift will be less likely to cause the loss of particular alleles: an equilibrium of a given stability under frequency-dependent selection will involve much stronger selection when gene frequencies are a long way from equilibrium than an equilibrium under an heterozygous advantage. The degree of stability of the equilibrium of the modifiers determines the rate at which a modifier can be selected for dominance. The stability of a genetic equilibrium may be measured by the proportion by which a deviation from equilibrium is reduced after one generation of selection. Suppose we have

genotypes:	AA	Aa	aa
frequencies:	p^2	$2pq$	q^2
fitnesses:	$1-c$	1	$1-d$

At equilibrium $p = d/(c+d)$ and $q = c/(c+d)$. If there is a small deviation from equilibrium such that $p = d/(c+d) + x$ and $q = c/(c+d) - x$, then it is easy to show that after a generation of selection x is reduced to

$$x' = x(c+d - 2cd)/(c+d - cd).$$

The value of $(c+d-2cd)/(c+d-cd)$, therefore, measures the stability of the equilibrium maintained by the heterozygous advantage.

If frequency-dependent selection maintains the modifiers at equilibrium, we have on the simplest model giving an equilibrium of $p = 0.5$,

genotypes:	AA	Aa	aa
frequencies:	p^2	$2pq$	q^2
fitnesses:	$1-kp^2$	$1-2kpq$	$1-kq^2$

This model is less general than the previous model of frequency-dependent selection in that the focal frequencies have not been specified: k is not therefore equivalent to K as a measure of the intensity of the selection; when one genotype is very common and the others are rare k has the same meaning as a simple selective coefficient favouring the rare genotypes. CLARKE and O'DONALD (1964) showed that for a small deviation from equilibrium, x, we have

$$x' = x(8-4k)/(8-3k).$$

Therefore if an equilibrium maintained by frequency-dependent selection is to be as stable as one maintained by an heterozygous advantage, then

$$(c+d-2cd)/(c+d-cd) = (8-4k)/(8-3k).$$

If $c = d$ and terms in cd are negligible, then $k = 4d$. The previous calculations showed that an heterozygous advantage of more than 0.0004 would stop the evolution of dominance of a mimic at an equilibrium frequency of 0.02—the frequency of the dominant form *leighi* in South Africa. Therefore, if the modifier is maintained by an heterozygous advantage, its selective advantage when it first arose by mutation was certainly not greater than 0.0004. But if it is maintained by frequency-dependent selection, its initial selective advantage was not greater than 0.0016. FISHER (1930) showed that a single mutation with a small selective advantage a has an ultimate chance of survival of about $2a$. Thus to give a final equilibrium of a given stability, a new mutation has four times the chance of survival by frequency-dependent selection that it has by an heterozygous advantage. And in the course of fluctuations in the size of the population, a gene at a frequency-dependent equilibrium will not be so liable to extinction by genetic drift opposing what is anyway very weak selection. If for ecological and physiological reasons, therefore, frequency-dependent selection be just as likely to occur as heterozygous superiority, then modifiers maintained by frequency-dependent selection should be four times as common as those maintained by heterozygous advantages because they will be four times more likely to survive as new mutations. Of course, against this, it may very reasonably be doubted that frequency-dependent selection often maintains polymorphisms.

Electrophoretically separable proteins are the evidence that populations are polymorphic at more than about 30% of the total number of loci (LEWONTIN and HUBBY 1966; JOHNSON *et al.* 1966; HARRIS 1966). Many of these loci may have modifying effects on quantitative characters. Heterozygous advantages could theoretically maintain the polymorphisms provided the selective coefficients are small and the loci are not independently affecting fitness (SVED, REED and BODMER 1967; KING 1967; MILKMAN 1967). Large selective coefficients or loci

acting independently on fitness would give rise to very great variations in fitness: the genetic load would be intolerable. But as YARBOROUGH and KOJIMA (1967) point out, frequency-dependent selection will not give rise to great variations in fitness when the genotypes are equal in fitness at equilibrium. Therefore if the selective coefficients of the modifiers are as small as I have suggested in this paper, then frequency-dependent selection would oppose genetic drift more strongly than an heterozygous advantage when a modifier is rare, but would not produce great variations in fitness when modifiers at many loci are common and at equilibrium.

Putting aside the question of how the modifiers are kept in a population, the calculations in this paper suggest that if a mimic in equilibrium at a low frequency is to evolve dominance, then the modifiers of dominance can be subjected only to very small pleiotropic selective forces. If these forces are not very small, the evolution of dominance will soon stop. The modifiers of dominance may therefore fall into that large class of nearly neutral mutations that KIMURA (1968) has shown must exist. They will be the ones that modify the expression of the heterozygote to determine its variability and degree of dominance. It may therefore be that at least part of the genetic variation of a quantitative character has but little effect on the overall fitness of individuals. That part of the genotypic variation will be available for the immediate selection of new adaptations in changed environments.

SUMMARY

Certain rare mimics of *Papilio dardanus* have evolved complete dominance over the more common mimics. A model of this evolution is set up in which the modifiers of dominance are held in the population by heterozygous advantages. The model shows that dominance can evolve only if the heterozygous advantage is very small—it can be no greater than 0.0004 if a mimic at an equilibrium frequency of 2% is to evolve dominance. In small populations the modifiers will therefore be liable to extinction by genetic drift. But frequency-dependent selection could also hold the modifiers at an equilibrium. Such an equilibrium would have to have the same stability as one maintained by a heterozygous advantage of 0.0004. If so, it can be shown that a modifier newly arisen by mutation would be subjected to frequency-dependent selection of four times the intensity of the selection by an heterozygous advantage. Frequency-dependent selection may therefore be responsible for keeping some of the modifiers in a population, for a single mutation would be four times more likely to survive by the frequency-dependent selection than it would by the heterozygous advantage. In general, if pleiotropic selective forces are acting on modifiers, they must be very small for

dominance to evolve. Thus it is likely that part of the genetic variation of any quantitative character is controlled by genes having little or no effect on fitness.

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