# THE POSSIBLE MODIFICATION OF THE RESPONSE OF THE WILD TYPE TO RECURRENT MUTATIONS

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## 1. *Gene Mutations*

THE very extensive series of gene mutations observed in *Drosophila melanogaster* and allied species is at present by far the most ample basis available for the study of these changes; nevertheless the nature of the mutant genes found in other groups may be cited as indicating that the outstanding characteristics of the *Drosophila* mutations may be characteristic of gene mutations in general. By far the most numerous classes are either (i) viable when homozygous, and completely or almost completely recessive, or (ii) lethal when homozygous. Of the latter class many are apparently completely recessive in their action, while in others the heterozygote is distinguishable from the wild type, showing so-called dominant characters. A third and much less numerous class are non-lethal dominants, in which, however, the dominance is usually incomplete.

I have listed, with some uncertainty, the non-lethal mutations of *Drosophila melanogaster* having visible effect, from the article of Morgan, Bridges and Sturtevant in *Bibliographica Genetica* (1), with the result shown in the following table:

| | Recessive | Incomplete dominant | Complete dominant | Total |
|---|---|---|---|---|
| Autosomal | 130 | 9 | 0 | 139 |
| Sex-linked | 78 | 4 | 0 | 82 |

The two alternative statements, that the mutant type is generally recessive, or that the wild type is generally dominant, are formally equivalent; nevertheless, the latter statement is to be preferred, in view of the behavior

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of series of multiple allelomorphs, of which *Drosophila* furnishes several examples, which have been admirably paralleled in the albino series in rodents. In these cases it is found that while the wild type is clearly dominant to the mutant allelomorphs, yet the heterozygote of two mutant allelomorphs is intermediate between them (1. p. 34). The mutant allelomorphs show little or no dominance *inter se,* although it has been demonstrated that one can arise as a mutation from another. This group of observations suggests, therefore, that it is rather a peculiarity of the wild type to be generally dominant than a peculiarity of the mutant to be recessive to the type from which it arose.

This feature in the behavior of multiple allelomorphs appears to offer a serious difficulty to the theory that the evolutionary adaptation of specific forms has taken place by the occasional and gradual replacement by mutant genes of the allelomorphic wild type genes from which they arose. For, in their dominance, the wild type genes appear to be clearly of a different nature from the mutant genes which arise from them. This difficulty will lose its force if it appears that there is a tendency always at work in nature which modifies the response of the organism to each mutant gene in such a way that the wild type tends to *become* dominant. It is the purpose of the present paper to examine this possibility.

## 2. *The Mutations Available for Study Are Probably Recurrent*

Enormous as is the number of experimental flies among which the *Drosophila* mutants have occurred, this number must fall short a thousandfold of the number produced in the wild state even in a single year. Unless great differences in the mutation rates are postulated, ascribable to the artificial environment, it follows that, when any mutation has occurred repeatedly under observation, we may be confident that this mutation occurs in nature with a frequency, at a moderate estimate, of some-

thing like a thousand times annually. As to the period during which this process has continued, we may best judge by the fact that homologous mutations have been proved to occur in different species. This fact gives us only a lower limit, since more distantly related flies have not yet been sufficiently examined, and, where crossing can not be practiced homology can not absolutely be proved. The occurrence of albino mutants in very different mammals suggests at least that this mutation has been occurring since an early stage in the differentiation of the group.

With respect to the majority of the *Drosophila* mutations which have occurred only once under observation, it is also probable that each has occurred with enormous total frequency during the history of the species, for this would be the case even if the frequency of mutation was only one in $10^{12}$, while a mutation occurring so rarely as this would have a very small chance of being detected in an experimental sample, which does not much exceed twenty-five millions; and we should expect to have detected few or no such mutants unless they were an enormously numerous class widely sundered in mutation frequency from the smaller group which are known to be recurrent. Such a view seems extremely improbable in contrast with the view that the majority of the mutations which we can hope to observe in experimental cultures, unless they can be ascribed to cultural conditions, are mutations of which the species has at least very extensive previous experience.

3. *Modification of the Reaction in Experimental Cultures* That such experience is capable to leading to a modification of the reaction of the species to the mutant gene is shown by an important fact which has now been repeatedly verified. Mutant types which have been kept as stock for several generations have been observed to show their mutant peculiarities in a materially lower degree than at their first appearance. This remarkable phe-

nomenon has been ascribed to the differential survival of the flies in the stock bottles, those having a hereditary composition which gives a mild reaction to the mutant gene having been more viable than those with a different hereditary equipment which reacted more strongly. That this view is correct is shown by the crucial experiment of mating these modified mutants to unrelated non-mutant stock, and extracting mutant flies from the offspring by inbreeding. It is found that this procedure restores to the mutant type much or all of its former pronounced character. The experiments demonstrate two points on which we shall rely: (i) that it is not the mutant gene which is modified but other hereditary factors which influence the reaction of the organism to the mutant gene; (ii) that those modifying factors which influence the viability of the mutant type do so in such a way as to influence *pari passu* its external characteristics.

The first of these points is essential to any theory of the modification of the response of the organism to a particular mutation, for the previous mutant genes must sooner or later all become extinct, and any mutant gene observed to occur in culture is in any case unmodified; whereas, since mutant individuals, heterozygous or homozygous, will leave a certain proportion of non-mutant descendants, the selection of modifications in the mutant types will affect the frequency of the corresponding modifiers in the population at large. The second point is of importance in showing that natural selection in such types, although based solely upon survival in competitive conditions, may be expected to modify those external characters, by the appearance of which, in the heterozygote, we judge which of the homozygous forms is to be called dominant.

4. *Selection of Modifiers in Natural Conditions*

In natural conditions we may assume that any type materially different from the wild form, such as the homozygote mutant, or the heterozygote if the mutation

is not almost completely recessive, will be at a disadvantage. For purposes of calculation we may express the whole of this disadvantage as though it depended merely on viability, that is, on the frequency with which the fertilized ovum survives to reproduce, any disadvantage in such characters as mating instincts, fertility, or instincts governing oviposition being expressed as an equivalent failure of viability. For simplicity we may also assume that mating is at random, at least in the sense that the choice of a mate is not affected by the gene in question. In these circumstances it is obvious that if the mutant gene is kept rare by counter-selection, the homozygous mutant type will always be very much rarer than the heterozygote. The actual frequency of each type will depend on the intensity of the counter-selection, the frequency of mutation being regarded as constant. If the heterozygote is in any appreciable degree less viable than the wild form, any counter-selection, exerted against the homozygote mutant, even complete lethality, will be of no importance in determining the frequency ratio of the genes at which the opposing influences of mutation and selection come to an equilibrium. Thus if one wild type gene in a million mutates in each generation, and v stand for the viability of the heterozygote as compared to the wild type, the relative frequencies of the three possible types will be, homozygote mutant, $p^2$, heterozygote, 2p, wild type, 1; where p is given approximately by the equation

$$p = \frac{10^{-6}}{1 - v}$$

or, in general, if k stand for the mutation rate, supposed small, by

$$p(1-v)=k$$

At one extreme, if v is a small fraction, p is nearly equal to k, and the heterozygotes will occur two million times as frequently as the mutant homozygotes; at the other extreme if v = 0.99, so that the heterozygote is only at a one per cent, disadvantage, the heterozygotes will still be twenty thousand times the more frequent.

These very high ratios justify the conclusion that if the *heterozygote is at any appreciable disadvantage compared to the wild type, it will be so enormously more frequent than the homozygote that any selection of modifiers which is in progress will be determined by the reaction of the heterozygote.*

Two other circumstances serve to increase the disproportion of the selective effects. In the first place, the efficacy of the selection in modifying the characteristics of the species depends not only upon the frequency of the individuals selected, but upon their chance of leaving a remote posterity. In fact we need to evaluate not the relative numbers of the two types in any one generation but the proportions they represent of the total ancestry of a distant subsequent generation. Evidently, if, as is to be anticipated, the viability of the homozygous mutant is lower than that of the heterozygote, the latter will count for more in future generations, and even if the two types had equal viability, the heterozygote is still at an advantage, for mated to a wild type only half his offspring will be heterozygous, while in similar case all the * offspring of the heterozygote will be equally handicapped.

This point becomes of importance with sex-linked factors when the mutant type males and the heterozygous females do not differ greatly in frequency, but may differ greatly in viability, with the result that the latter may occur much more frequently in the ancestry of the existing wild population.

In the second place there is some evidence that the heterozygote is naturally more modifiable than are the homozygous types. How much weight should be given to this consideration, it is not easy to say.

The fraction of the ancestry of future generations ascribable to heterozygotes, though greatly exceeding that due to mutant homozygotes, is still exceedingly small, it may be expressed approximately as

$$\frac{2p(p-k)}{p+k}=\frac{2kv}{(1-v)(2-v)}$$

* For heterozygote, read homozygote.

and this represents the ratio of the rate of change to be expected in nature to the rate of change which could be effected by exposing a population composed entirely of heterozygotes to selection of the same intensity. This fraction is, of course, extremely small; if k is $10^{-6}$, its value is only a trifle greater if v = ½, rising to about one five thousandth if v is as high as 0.99. Nevertheless, considering the ratio of the periods of time available it seems not impossible, but rather probable, that the reaction of the wild type to the heterozygous phase of a recurrent mutation has in some cases at least been modified to an appreciable extent.

The efficacy of selection in modifying the heterozygous type of an imperfectly dominant mutation is open to experimental verification, and some idea could thereby be obtained as to the possible speed of the process. There is one respect, however, in which it will certainly be difficult to allow the experimental conditions to do full justice to the natural conditions which they simulate. The intensity of selection acting on any particular modifying factor would have to be perhaps 100,000 times greater than under nature. It would be difficult to prevent selections of this intensity from depleting the supply of modificatory variance available in any small experimental group of flies, and in consequence the efficacy of selection, if the experiment were prolonged beyond a few generations would fall off from a cause which would have no parallel in the natural evolution of the species. The maximal rate of progress observed might be expected to supply a better estimate than the average over a considerable period; though the latter doubtless would be easier to observe with precision.

It will be noticed that the fraction calculated above decreases very rapidly as v ? 0, and also increases very rapidly as v ? 1. The early stages in the improvement of the heterozygote will necessarily be retarded very much more severely than the later stages, which may be expected to be passed through quite rapidly in compari-

son. Heterozygotes, the viability of which is much impaired will thus have made no appreciable progress by the time that others less heavily handicapped at the start will have become completely normal, in viability at least, and presumably also in appearance. Whatever were the relative frequencies of dominants, recessive and intermediates of various grades among mutations at their first occurrence, we should expect, if the above selective process has had time to produce great effects, to find that the greater number of recurrent mutations had become completely recessive. And this is what appears to be the case, in *Drosophila* and, with some exceptions, in other organisms generally. A certain number of cases should, however, be found, if the survey is carried sufficiently far, in which the reaction of the organism to the mutant gene is nearly in its original condition, either because the mutation is really of comparatively recent origin, or because it affects the chances of life so seriously, in the wild environment, that no appreciable progress has been made in its modification.

5. *Modification of the homozygote*

Until the heterozygote has attained practically normal viability, there will be no appreciable tendency for the reaction of the organism to the homozygous mutant to be modified, except in so far as some such an effect has already been produced by the selective modification of the heterozygote. The last stages in the approach to normal viability will be carried out comparatively rapidly, for the intensity of selection itself varies inversely to 1 — v; during these final stages p increases very rapidly so that the numbers exposed to selective action not only of the heterozygote, but of the mutant homozygote will be very greatly increased.

If a stage is reached at which the heterozygote survives absolutely as well as the wild type, the frequency of the mutant gene will begin to depend upon the viability of the homozygote; if w stand for the viability of this geno-

type, the condition of equilibrium corresponding to equation I is

$$p^2(1-w) = k, \qquad \text{II}$$

while the fraction of the ancestry of a remote posterity which in any one generation are homozygotes will be

$$\frac{kw}{1-w}$$

If w is small it is seen that the rate of progress at this stage is the same as that of a heterozygote of the same viability; so long at least as this progress is so slow that the rate of increase in the number of mutant genes is small compared to the rate of mutation. It is only necessary to note that this process can not commence until the viability of the heterozygote is, within a very minute fraction, equal to that of the wild type; and that if w is not small we are approaching a condition in which the mutation rate is not balanced by counterselection, and in which other considerations, such as reverse mutations, cease to be negligible.

It is clear, however, that a persistent mutation in which even the homozygote has not too bad a chance of survival, the homozygote may follow in the footsteps of the heterozygote, and become indistinguishable from the wild form. Such mutations might in fact leave no trace for genetic research to reveal. The sex chromosome provides the best opportunities for such a complete obliteration.

6. *The pristine character of the reaction of an organism to a gene mutation*

We should, on the view developed above, expect to find the appearance of the heterozygote of two alternative genes, in its original condition, only in somewhat exceptional cases.

(i) The occurrence of a mutation which is really comparatively new in the history of the species;

(ii) Mutations in which even the heterozygote has had from the first an exceedingly small chance of survival;

(iii) Different mutations of the same gene, which can be brought together experimentally, but which can seldom have come together in nature; (iv) Specific modifiers producing no external effect save in the presence of mutant genes in other loci.

It can scarcely be hoped that more than a very small proportion of mutations occurring in experimental cultures can belong to the first class. Clearly, Muller's success, in multiplying the mutation frequency by means of X-rays, gives the best hope in the direction of securing mutants which have seldom occurred before. If, on the other hand, the adaptive modification of domestic varieties of animals and plants has taken place by the accumulation of favorable mutations, a certain number of comparatively new factors should be found to distinguish highly selected varieties from more primitive varieties of the same species; though even here it is not impossible that use may often have been made of old mutations which had repeatedly occurred and been rejected as unfavorable in the wild condition.

It seems possible to regard the dominant mutations in *Drosophila* as, for the most part, cases in which the chances of life of the heterozygote in the wild state are so low that no appreciable modification has taken place. If this is the case it may be significant that the dominance is usually, if not always, conspicuously incomplete, the homozygote being either lethal in its action, or exhibiting a more pronounced effect than the heterozygote.

The heterozygotes of allelomorphic mutants show a strong tendency to lack dominance altogether. Wright's quantitative study (2) of the albino series in guinea-pigs shows this effect very clearly. Morgan, Bridges and Sturtevant (1) give the rule as general for *Drosophila melanogaster,* though possibly there are exceptions. These certainly exist, though they are rare, in other organisms; thus the Himalayan allelomorph of the albino series in rabbits is dominant to the complete albino. Instances are rather numerous in the literature of one

allelomorph being spoken of as dominant to a second, when in reality the heterozygote is clearly intermediate; this loose use of the term makes it difficult to summarize the evidence of the several multiple allelomorph series found in mammals. Such evidence is, however, in any case on a different footing from that drawn from the *Drosophila* mutations, for some of the genes involved in domesticated varieties have been exposed in large numbers to the selection of fanciers, and in some cases it even appears that the heterozygote has been particularly selected by the fancier to conform to his ideal.

In opposition to the view suggested by the above classes of facts that complete dominance is not characteristic of the reaction of the wild type to a mutation at its first appearance, the specific modifiers seem often to show complete dominance. Thus of 6 modifiers of eosin eye color which have no visible effect on the wild fly, Bridges (3) finds only one with intermediate heterozygote, the remaining five being ordinary recessives. Since it is not easy to see how dominance in such cases could be brought about by selection in stocks in which the eosin eye only occurred as a rare mutant, such cases as these seem to indicate that for the mutant condition to be completely recessive to the wild type is a frequent occurrence from the start, though possibly less frequent than the proportion of recessive mutants observed in *Drosophila* would suggest. A comprehensive summary of the behavior of specific modifiers from this point of view would be of very great interest.

Finally, the possibility discussed above that the dominance of the wild type is in some cases a product of evolutionary change in the manner outlined throws no light upon such a case as is presented in poultry, where a majority of the genes which distinguish domesticated races from the wild type appear to be non-lethal dominants.

7. *Summary*

The consideration that the wild population is immensely larger than the numbers bred experimentally

even in *Drosophila*, and that the duration of the species is still more disproportionate to the experimental periods, leads to the conclusion that the majority of the mutations which we can hope to observe in cultures must have occurred previously with very great total frequency in the wild species.

The reaction of the wild type to mutations is known in many cases to be capable of a somewhat rapid modification in experimental conditions, by the selection through differential viability of factors capable of modifying this response.

It may be calculated that with mutation rates of the order of one in a million the corresponding selection in the state of nature, though extremely slow, can not safely be neglected in the case of the heterozygotes.

The observed behavior of multiple allelomorphs largely supports, though that of specific modifiers seems to oppose, the view that complete dominance generally may be regarded as a product of such selective modification.

## LITERATURE CITED


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