ON THE INCOMPLETE DOMINANCE OF THE NORMAL ALLELOMORPHS OF WHITE IN *DROSOPHILA*.

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(With One Text-figure.)

On the basis of the dosage compensation phenomenon exhibited by most mutant allelomorphs of the white eye series, rendering the male and female nearly the same in shade despite their different doses of the locus in question, the conclusion was drawn (Muller, 1932) that the normal allelomorph, non-white ("red"), must have the same property, and that the evolution of this property by natural selection could be explained only on the premise that, given the same genetic residuum, one dose of the normal allelomorph ordinarily produces, even to-day, a lesser effect than two doses. Such a difference in effect is not visible, yet must still be great enough to be of importance in survival, otherwise the dosage compensation mechanism would degenerate. Inasmuch as the mutant allelomorphs in question are hypomorphic (having lesser effects than the normal, *i.e.* effects like those produced by reduction in dosage of the normal gene), the above conclusion could be expressed by saying that the normal gene, although apparently quite dominant to white and to the other mutants, must in reality be incompletely so, and the heterozygotes, being like uncompensated hemizygotes,[2] must have a definitely lower average survival rate. The survival value must in fact be so low that, in populations in which as much as 50 per cent. of the individuals have the composition (heterozygous or hemizygous) that is subject to this weaker grade of character expression, the selection pressure thereby resulting is great enough to overcome any contrary mutation pressure and any other tendencies towards dispersive (non-directive) evolution, and to force evolution in the direction of compensation of the unfavourable

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[2] The terms "hemizygous" and "hemizygote" (Serebrovsky) refer to the condition of being haploid for a given gene when the genome as a whole is diploid; its usual usage is in connection with sex-linked genes in the sex in which they are haploid.

effect; the compensation, once attained, would also be actively maintained against the same dispersive tendencies. The mechanism of establishment and maintenance of the dosage compensation is in some ways like that postulated by Fisher for dominance, but a far larger proportion of the population is subjected to this more special kind of selection.

To demonstrate the existence of this imperfect dominance more directly, quantitative pigment studies were attempted, but the standardisation of the technique of extraction of the pigment offered considerable difficulty. Bridges' observation made in 1913 may be recalled, however, that in the simultaneous presence of the mutant genes vermilion and pink, non-white is visibly incompletely dominant to white. Pursuing the attack further, with the background of normal genes in other loci, triploid females having white (which is virtually "amorphic") in two of their X's (attached) and non-white in their third X (free) were made up. These proved to show a distinct deviation from the normal red, as seen in either triploids or diploids. The coloration partook of the character of the least deviant allelomorphs of the white series, such as wine and blood, although it was still nearer to normal. It thus gave the superficial effect of actually being somewhat darker than normal, as these allelomorphs too sometimes do—probably on account of the lesser amount of red reflecting pigment in the thin ommatidial walls allowing the darker depths of the eye to be more easily seen. When newly hatched, however, the eye was lighter than normal, and of the characteristic pinkish colour likewise to be seen at that stage in the allelomorphs mentioned above. Hence it is reasonable to conclude that the amount of pigment does vary with the dosage of the normal allelomorph, being visibly less at a dosage which is one-third that of the normal; but that in the case of the half-normal dosage, the amount of pigment already lies above the critical level beyond which the differences in amount are no longer, or are hardly, discernible to the human eye. Hence the curve of variation of the visible effect (colour) as the dosage increases (representing the former as the ordinate and the latter as abscissa) is a curve that draws very near the horizontal before the half-normal dose is attained (see Fig. 1).

On the basis of this result, it was decided to test out in the same way the two different normal allelomorphs of white which had been shown, in the notable work of Timoféeff-Ressovsky (1932), to have different frequencies of mutation to white when irradiated. It may be recalled that in some of his experiments the genetic residuum had been made the same by repeated crossing. The normal allelomorph derived from an American stock, when in combination with this residuum, showed twice as frequent

mutation to white, although about the same frequency to the less extreme mutant allelomorphs, as did the normal allelomorph derived from a Russian stock. Moreover, a change of the genetic residuum did not affect these mutation rates perceptibly. At the same time, the two normal allelomorphs seemed phaenotypically alike. We received stocks of the two allelomorphs, which had already been repeatedly back-crossed to the same stock to give them the same residuum, from Timoféeff-Ressovsky, and we crossed them to our triploids having white in their attached-*X* chromosomes. The triploid offspring in both cases gave the pinkish eye colour when first hatched, but in the case of the Russian allelomorph this soon changed through maroon to a typically normal red colour, whereas in the case of the American allelomorph the colour became and then remained of the maroon-like sort above referred to, recalling that of the darker mutant allelomorphs.

The result clearly shows that the American allelomorph, which mutates more readily to white, has a lower degree of dominance, and, speaking more generally, a lower degree of activity or effectiveness in pigment production, thus standing functionally lower and nearer to white. This illustrates the kind of difference referred to by Haldane in his paper (1930) pointing out that dominance may sometimes have originated through selection of more potent "normal" allelomorphs, arising by mutation at the locus in question. It also illustrates his contention (1932) that in such cases the more potent allelomorph brings about the production of the (apparently) maximal phenotypic effect earlier in the course of development. In the present case, however, there is no evidence indicating which allelomorph should be regarded as nearer the condition of the common ancestor.

In this connection it must be pointed out that, while the general level of activity or dominance of a normal gene in a given race or species probably was attained in part in the way suggested, *i.e.* through a process of natural selection that chose between more or less invisibly different mutations of the same locus (multiple allelomorphs), nevertheless this by no means implies the correctness of Fisher's view, that the degree of dominance *in itself* was the important matter in the selective process, and, through its effects on the survival rate of heterozygotes, determined the course of evolution. The degree of dominance was probably only a secondary concomitant or reflection of the general degree of activity ("potency") of the gene, as I have elsewhere pointed out (1932), and as has been maintained independently by Plunkett (1932), and the value of having this degree of activity above a certain critical level, at or near

which visible dominance in the heterozygote is attained as a secondary effect, lies in the protection thus afforded the individual against disturbing genic and exogenic influences other than heterozygosis and collectively much more important than the latter, which would otherwise suffice to cause visible deviations of the character in question. In the present instance, the greater susceptibility of the visible character to genically and exogenically induced changes in its degree of expression, when the activity of the gene lies below the critical level of dominance, is well illustrated by the higher variability of the eye colour resulting from the intermediate allelomorphs, such as eosin, apricot, blood, etc., than that resulting from either of the known normal allelomorphs.

The fact of dosage compensation in itself provides a direct verification of our present contention that, given the existing curve of effect, there is a distinct survival value—quite apart from any protection of heterozygotes—afforded by the possession of gene potencies more than twice as great as those necessary to give the maximal visible effect, *i.e.* such selection operates, without the intermediation of heterozygotes, to maintain potencies sufficient for dominance. For in the male there can be no question of protection from the effects of heterozygosis, and yet, by means of the accumulation of specialised modifiers ("compensators"), the male with its one dose of the normal allelomorph has been brought to the same high degree of gene activity as the female with her two doses. This would not have happened if this high degree of potency had not been important for survival in the male, and the selective advantage of these "compensators" could certainly not have lain in any effect on heterozygotes, since the male (in which alone they find the expression in question) cannot be heterozygous. In this case, be it also noted, the evolutionary process has necessarily consisted in the selection of "modifying genes", and not in the selection of such "normal" allelomorphs of white as had a higher potency.

All this, however, would still leave open another question. Why should it be that the point on the curve of character expression-gene dosage (Fig. 1) which represents the most advantageous degree of character expression for the organism, should happen to be in that region where visible dominance has (just) become complete, *i.e.* where a halving of the dose would still leave the character (just) above the critical level of visibility? On Fisher's view we should have to say: because modifiers have been selected, through their favourable effect on heterozygotes, which give the curve this shape (or, to put the matter in another way, which alter the effectiveness of the gene so that the

favourable potency lies at this point in the curve). On our view, we should say that this portion of the curve is correlated with the greater stability of character expression needed, and hence, if the original gene potency were not such as to exhibit this dominance, modifiers and allelomorphs would have been selected which caused the advantageous degree of effect to be produced by a degree of potency lying in this part of the curve.

It would be interesting to know whether the nearness of the normal potencies here studied to the critical level necessary for visible dominance (as shown by the visible intermediacy of the one-third normal concentra-

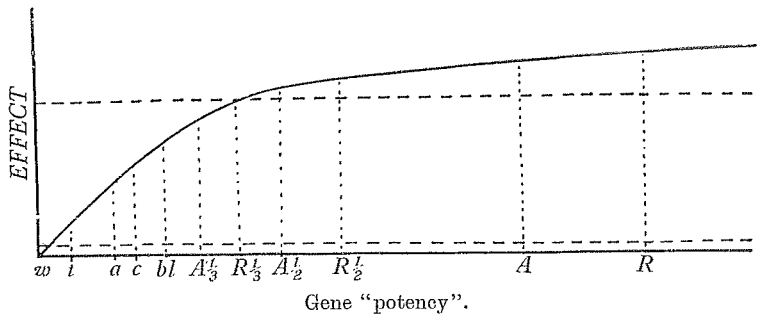

Fig. 1. Proposed schematic curve showing relation of the amount of pigment formation (the ordinate) to the degree of total gene activity (the abscissa) in allelomorphs of the white eye series. Upper horizontal dashed line represents the upper critical level of coloration, above which differences in the shade of (red) eye colour are practically invisible. Lower horizontal dashed line represents the lower critical level of coloration, below which differences in the shade of (nearly white) eye colour are practically invisible. The points representing the estimated degrees of gene activity are marked for the following cases:
t = homozygous tinged female or hemizygous male (approximate).
a = homozygous apricot female or hemizygous male (approximate).
c = homozygous cherry female or hemizygous male (approximate).
bl = homozygous blood female or hemizygous male (approximate).
A = homozygous normal female or hemizygous male (approximate) (of American type).
R = homozygous normal female or hemizygous male (approximate) (of Russian type).
$\frac{1}{2}$ = heterozygous diploid female of type designated (*i.e.* one-half dose).
$\frac{1}{3}$ = triploid female with one gene of type designated (*i.e.* one-third dose).

tion) is accidental or represents a general tendency in genes. This is a matter that can and should be tested experimentally; in fact there is probably sufficient information on gene expression in triploids already extant (chiefly in experiments of Anderson and of Redfield) to answer this question, if the data be re-examined. If this should turn out to be a general tendency we should probably have to explain it by some principle of economy in organisms—*i.e.* that a superfluity of substances or reactions is apt to be burdensome, and disturbing to other processes, and by

the further principle that mutation pressure tends in general towards inactivation (Muller, 1927, see pp. 259–60; Wright, 1929).

In his very illuminating recent analysis of dominance, which the present author read only after all the above had been written, Wright gives cogent evidence, based mainly on considerations of the course of chemical reactions in morphogenesis, for the conception that dominance is to be expected as the more usual phenomenon, even before selection has had a chance to modify it. If we may paraphrase in our terms what seems to us the chief principle involved in his discussion, we would say that the nearly horizontal "right-hand" part of the gene-character curve (of which he gives figures similar to our independent one given here)—the part in which practically complete dominance is found—is far longer than the initial part, which gives intermediate heterozygotes; therefore it is very likely, *a priori*, that the potency of any given gene shall be at some point in the right-hand part, and shall thus be sufficient for dominance. Selection for dominance, of the sort which I have postulated, would, then, seem to enter in only in the rarer cases where the potencies originally lay in the small "left-hand" part of the curve. But if there is a principle of "economy", and one of mutation pressure towards inactivation, as would be indicated if most normal genes, like the ones dealt with in the present paper, show intermediacy when in the one-third normal concentration, then, despite the truth of Wright's general thesis, selection of the type advocated by Plunkett and myself (*i.e.* towards a "factor of safety") would finally have to enter again, to hold the potencies up to a level which would automatically be adequate for dominance.

The results of the present tests further illustrate the fact that there is a certain leeway in selection, allowing for the existence of two different types of the normal allelomorphs themselves. For it is likely that one or the other of these became established by a process of accidental survival and multiplication, rather than as a result of divergent selective processes based on significantly divergent conditions of existence of the two races. But such comparatively great differences in gene potency between different races must be rather unusual (unless they are compensated by modifiers, which was not the case in Timoféeff-Ressovsky's races), for if they were common we should not expect the dosage compensation to be as accurate as it usually seems to be. For the accuracy of the dosage compensation is another criterion by which we may measure the rigorousness of selection in discriminating between, and establishing, given grades of potency, and this indicates, in the present case (judging by the dosage compensation shown by most *mutant* allelomorphs of the present series), a

degree of discrimination about on a level with our own powers of vision of differences between intermediate allelomorphs.

It would be of interest to know whether the mutation frequency of the American allelomorph is really higher, as it seems to be, or whether the apparently higher rate is merely the result of more of its mutations being within the visible range, while more of those of the Russian allelomorph result simply in less potent "normal" genes, like the American allelomorph itself. If the latter suggestion is correct, then, since the number of visible mutations to intermediate-coloured non-white allelomorphs is approximately the same in both, we might regard the whole scale or "spectrum" of mutations as being shifted towards white in the case of the American allelomorph. When the mutational "spectrum" was thus shifted, more mutations would be caused to be heaped up at the *O* value of potency.

Not only the red region of this scale, but also the white region, could conceivably occupy a certain range of "potency", although differences within it are not distinguishable to the eye. It is likely, however, that this range is very small, not only in view of the consideration that a sigmoid gene-character curve would require a more specialised set of developmental reactions, but also judging by the facts that compounds of intermediate allelomorphs with white seem to have roughly half the amount of pigment of the corresponding homozygote, and that different effects in compounds with different whites have not yet been established (in the author's own tests, the Notch 8 deficiency for the locus of white gave compounds like those of the usual white mutant).

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