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Svalöf.

14/5/34.

Dear Professor Fisher,

There are a number of points of interest raised by the reprints which you sent to me, particularly in connection with the theory of dominance evolution.

I like your theory of selection among the modifiers of intermediate heterozygotes leading to dominance but there are one or two points which I should like to raise in this connection.

As regards the effect of human selection in domesticated organisms I am convinced that selection of modifiers has played a very important role. If your experiments with hens work out as successfully as you expect, I think that it will provide a very elegant demonstration of how the dominance of certain genes evolved in an unusual manner as a result of selection in an unusual population.

However I feel that the question of dominance in wild populations is much more speculative, at present. Sewall Wright's theory, as expounded in a recent number of the American Naturalist, seems to me to be too sound to be lightly dismissed. His idea receives support from a rather unexpected direction viz. the behaviour of quantitative characters which, as Dr. Rasmusson (Hereditas 1933) has shown, strongly indicates factor interaction in the same way as Wright postulates for the two homologous genes. I think that it must be granted that will be a general tendency towards dominance no matter whether there are modifiers or not. The degree which such dominance will reach is, however, more speculative and will probably vary in different cases. However, if an all-or-none reaction is included in the train of events, dominance must be complete.

Such a physiological theory does not and cannot preclude the possibility of selection of modifiers as Wright himself grants, although he draws what seems to me to be a rather fine distinction between different types of selection.

I have not space to review all the evidence form the points of view of the two theories but I think that there are a few particular instances which are of more than unusual interest in this respect, which might very profitably be considered.

First of all there are the eye colour suppressors in Drosophila. Presumably on your theory the eye colour mutants are recessive on account of some disadvantage in the intermediate heterozygotes having been selected against in the past. So it seems to me that it should then follow that any gene which exerts no other effect than to suppress the effect of such

eye colour genes should not be disadvantageous but rather tend the opposite way. Hence one would expect the suppressor genes, ~~at least~~ at least to show intermediate heterozygotes. The actual experimental results show, however, that all the suppressors are themselves recessive, in fact one wild type allelomorph will override the effect of two of the suppressor genes. (Bridges and Schultze, Amer. Nat. 1930). I cannot quite see how such a result would follow on your theory, unless it is postulated that the suppressors affect other characters adversely and, of course, it must be granted that they are sex-linked, which will affect the conditions under which selecting agents would work. On the other hand such a result would follow very easily from an interaction hypothesis such as Wright's. Suppose, with Wright, that the gene is the controlling influence of certain reactions in a chain of events. Then the effect of the eye colour mutants might be to reduce the speed of some link in that chain of reactions. Then the suppressor might be supposed to speed up the reaction at some previous stage in such a way that the net result is as before, as regards the eye colour. This would furthermore lead one to expect some small difference between the wild type and the type with recessive eye colour mutant and suppressor present, since it seems improbable that the two effects would entirely balance one another. This is I think what Schultze (Proc. Nat. Acad. Sci. 1930 or '31) finds. (I cannot get hold of his paper to check this statement as that journal is not in the library here, so I am working from memory at this point).

Next turning to the case of the so called 'dominant" mutations in Drosophila, on your theory they should show intermediate heterozygotes because there has not yet been selection of the modifiers which would make for dominance of the wild type allelomorph. This could follow from (a) the intermediate herterozygotes not being deleterious to the fly (b) from the mutation having been too infrequent for selection to have had the necessary scope or (c) from the gene pair being relatively new in the history of the species and selection not having had time to work to any extent. The situation does not however bear out these expectations altogether. In very few cases is the heterozygote as viable as the wild type. At least one such gene pair (Delta and its allelomorph) was presumably in existance before the separation of melanogaster and simulans since this mutation has been obtained, and proved to be the same, in those two species, and finally a number of these genes (again including Delta) have occurred as mutations more than once in culture, so showing that they have not been too rare as mutants for selection to operate unless it is supposed that they have different mutation rates now than before.

On the other side is the case, noted by Ford, of the effects of certain colour genes on the internal organs in Drosophila. I can see no easy explanation of this on a purely physiological hypothesis.

Of course in considering any such phenomena as dominance from a physiological point of view we are badly handicapped by lack of knowledge of how the genes work. Any such consideration must be of a rather speculative nature, but it does seem to me that dominance must be a product of both selection and general physiological tendencies rather than either by itself. The precise role of each in the evolution of dominance is impossible to analyse at the moment. In planning future work on the subject I think that it will be very necessary to work from both points of view. For example the physiological effect may perhaps be tackled by studying the effect of the same gene in two different sorts of protoplasm such as those of Vicia faba major and minor which Sirks has shown to be very different. Then there is the possibility of obtaining information by Muller's method of adding very small chromosome fragments containing the gene under consideration. From his lecture before the Genetical Society last year I gathered the impression that this may be a very useful line of work. It will of course require some knowledge of the effects of X- radiation on the chromosomes of the organism used, as X-rays seem to be the only way in which such fragments may be obtained. There are also a number of other lines of approach which suggest themselves, but which of course might prove to be impracticable, e.g. there is the chance of starting artificial selection in some way in which it would not occur in nature, but this would probably take too long, and there is the possibility of evidence being obtained by a study of the effects of genes which affect both morphological and physiological characters of the organism. One line of work which I am sure would be very useful would be to tackle the question of dominance in polyploids. It is quite conceivable that in allopolyploids, like wheat and oats, the modifiers do not get the chance to work properly on account of the corresponding genes in the "analogous" chromosomes. It is of interest to note in this case that certain characters in those two plants do show incomplete dominance (grain colour in wheat, chaff colour in oats) but with definite signs of factor interaction such as Wright's theory would demand. In other words if the effect of selection for modifiers is lessened, what dominance there is seems to be of a physiological nature (is incomplete). This would apparently indicate that in diploids dominance is of both types, as the Drosophila data reviewed above also indicates. This will also bear on Harland's case of the behaviour of crinkled dwarf in the Upland cottons. Cotton is polyploid (from Skovsted's work) but it seems to me that in that case the analogous chromosomes are very differentiated and so [illegible] the genetical behaviour

has returned
practically to that of a diploid. Harlands own results now show that the situation is not so simple as it first appeared and perhaps consideration from some such point of view as I have suggested may help to clear up the question.

Finally I think that one cannot overlook the effects of possible reduplication within the normal chromosomes of a diploid complement. Such reduplication seems on genetical grounds, to be present in Pisum although that is not yet proved. How far it occurs in other organisms is a matter on which we have little evidence. Catcheside's observations on the haploid Oenothera blandina, species which in the diploid forms only bivalents at meiosis, indicate duplications in the haploid complement, although some American cytologists would interpret his results as due to non-homologous chromosomes pairing - an explanation which I personally do not favour. This line of argument links up with Muller's work, quoted above, and perhaps may be approached in the same way. It does however seem to me that the cytological side cannot be neglected even in considering such purely genetical questions as dominance. Cytology can supply no information in itself but provides the necessary basis for the interpretation of the genetical results.

The cytological side is also prominent in the question of the polymorphic forms. Their behaviour fits in very beautifully with your ideas but I am concerned to know how the close linkage is brought about. It could be due to inter-chromosomal linkage due to translocations but the conditions which must be fulfilled, for such a mechanism to be good, are rather exacting. I feel that there must be made a very careful study of some such form from this aspect. If the snail chromosomes are at all suitable I think such a study would be well worth undertaking.

Leaving the theory of dominance now, I was interested in Winge's theory of the behaviour of doubleness in Stocks, as it marches so closely with the results of Philp and Huskins (Jour. Genet. 1931) who were able to show that the pollen lethal effect was due to one chromosome (the one with the single gene) being deficient for a trabant.

I also note, both from your stock and linkage estimation papers, that you are interested in the application of mathematics and mathematical devices to the extraction of fuller information from available genetic data I have, myself, been interested in the application of such methods to cytology - a subject which in my opinion is in need of fuller statistical treatment. Recently I have been able to demonstrate, by the use of analysis of variance a very significant negative intra-class correlation between the chiasma frequencies of the bivalents in the pollen mother cells of Secale cereale and Vicia faba. (This is paralleled by the increase in crossing over in one chromosome when it is jammed in the others by inversions in Drosophila). I think that the use of such methods [illegible] with the application of agents

such as heat, X-rays etc., which we know affect the chiasma frequency, we may obtain much information about the influences underlying the formation of chiasmata and crossing over. It is a problem on which I am working at the moment and one with which I should be considerably assisted by being in touch with mathematicians.

There is another use of mathematics which interests me considerably viz. for linking up cytological and genetical methods. Modern cytlogical theory is so far advanced as to rpovide us with a very good weapon for the attack of unusual genetical results. It is a line of work which requires a very good knowledge of cytological theory and genetics at the same time, and the ability to connect them up by mathematics. Hence it has been attempted by very few people. So far I have only used simple calculations but the results indicate what could be done by more refined methods. For example, in a paper, which I wrote recently (unpublished yet), I was able to show, on cytological grounds, that two genes lying in the same arm of a chromosome but showing no linkage as alternate dominant and recessive in the progeny, owing to the occurrence of more than 50% crossing over, will betray their positions by failing to show independence in their proportions of reductional and equational separation at the first meiotic division, if that can be studied. In one case where we have genetical data on the type of reduction, viz. in Bombyx mori, there does exist such a "reduction correlation" between the gene pairs N-n and X-Y, which are normally not showing linkage. The cytological theory of reduction also proved to provide the explanation of some of the $\hat{XX}$ data from Drosophila, and to be very necessary for a proper understanding of polyploid segregation. These results are, I think, of importance and , as I said before give some idea of what may be gained by extended analysis along these lines with the cooperation of a mathematician. In particular it may be possible to use such methods for detecting unusual types of cross over relations, such as chromatid interference, where it has hitherto been impossible.

In concluding I might mention something which I omitted above, viz. that I have a number of different wild strains of Drosophila melanogaster into which at the moment I am backcrossing a number of different genes from the normal mutant stocks. At least one of these wild strains is phenotypically very different from the standard wild type of the American workers. Although the backcrosses are being conducted from another point of view the results may be of interest in connection with the theory of dominance evolution.

I trust that you will excuse the somewhat disjointed nature of my comments. A full discussion of any one point would want a great deal more

space than I have at my disposal and so, of necessity, I have had to confine my remarks to the more salient features of the cases. I can only hope that at some future date I may have the opportunity of continuing the discussion with you, particularly on the subject of dominance evolution, which is a matter which attracts me strongly but which in the past I have never had the opportunity to talk-over, to any extent.

Yours sincerely

K Mather

(K. Mather)