

December 16th, 1935

Dear Professor East,

I have been puzzling over your recent paper on dominance, published in *Genetics*, vol.xx, p. 443, and write to tell you that, contrary evidently to what you have been led to believe, I agree with nearly all that you say there.

It is a disadvantage in writing on topics of interest on the other side of the Atlantic that one frequently finds one's views have been misapprehended, frequently, I believe, through opinions being carelessly ascribed in discussion to this writer or that, without an examination of what he has actually written on the subject.

For example, I have frequently expressed the view that the mutational material most fully studied by geneticists represents, from the evolutionary standpoint, the persistent failures among mutations. I am, therefore, generally in accord with your statement, p.447, that "defective genetic isomers are not the mutations that serve as material in evolution". Indeed, I have regarded my work on the evolution of dominance as affording evidence strongly corroborative of this view. But you say

immediately following, "Fisher found it necessary to formulate a theory of the evolution of dominance because he assumed that the mutations described for Drosophila gave a true picture of the mutations available for the differentiation of forms. If the assumption is false, the theory is unnecessary. I feel convinced that it is false". I, also, feel convinced that it is false, and have never before realised that I was supposed, at any point, to have assumed it to be true. It was certainly no such assumption that led me to formulate my theory of dominance. What led me to formulate this was only the body of observational fact respecting dominance found for those mutations which have been adequately studied by geneticists. This is none the less a body of fact, capable, as I believe, of an evolutionary explanation: whether or not one believes that these mutations are, as the earlier mutationists thought, effective material for evolution, or, as I strongly believe, almost wholly ineffective.

It was, of course, widely believed at the time, when the mechanical theory of evolution by mutations was advocated as an alternative to natural selection, that the recessiveness of mutations could be explained by the supposed facts (i) that mutations were mostly losses (ii) that losses were mostly recessive: and views akin

to this are still widely disseminated. You may recall my arguing in the first paper, 1928, which I wrote on the subject, that this view, presupposing immovable dominance relationships, is inconsistent with the prevalent rule of dominance in cases of multiple allelomorphism. In strict logic this argument only proved that one or other of two propositions, both, I believe, false, was untenable: (a) that the mutations useful to the evolutionary process display universally dominance phenomena similar to those found in ordinary genetic material; (b) that dominance relationships are the necessary consequences of the biochemical properties of the genes displaying them. To anyone assuming (b), and this certainly was the prevalent assumption in 1928, it would be natural also to assume (a), whether or not he thought that the available genetic material was actually of evolutionary utility. He would be judging of the unknown by analogy with the known, as in fact we always do when there is no clear reason against it.

As soon, however, as it is admitted that dominance, like the other properties of living organisms, is capable of evolutionary modification, it becomes obvious that we have no right to judge of the dominance phenomena shown by new, and possibly advantageous, mutations, from those shown by a group of mutations evidently for the most part

ancient, and disadvantageous over a wide range of conditions. If I remember right, I distinctly suggest in the same paper that, in view of the facts adduced, it would be reasonable to infer that new mutations showed neither dominance nor recessiveness as a general rule, but would have, for the most part, intermediate heterozygotes. For those who agree with me it follows that the same should be true for all genic differences which have not had their dominance relationships modified by persistent selection. This persistent selection has certainly occurred against all ancient deleterious mutations with sufficient mutation rates, and will have occurred also, usually much more rapidly, in some polymorphic species and domestic varieties, where the heterozygotes are exposed to selection in much greater numbers. You must have overlooked these parts of my paper and of later papers on the same subject in writing "Fisher simply accepts without question the postulate that nearly all mutations are recessive to wild type". I accept only the observation with its limitation to available genetic material. One of the novelties of my 1928 paper was to suggest the contrary of the postulate that the same is true of non-deleterious mutations or of those yet untried.

I may say that I have quite an open mind on what you call the one physiological implication of my theory, namely, that the heterozygote is inherently more modifiable than either homozygote. On biochemical grounds this certainly seems to me probable a priori, and there are a large number of rather insufficient facts which support it. Experimentally it seems usually to be masked by an effect, probably of more importance namely the greater variability of mutant as compared with wild genotypes. I much distrust a priori biochemical reasoning, owing to our profound ignorance of the chemical situations possible in the cell. Since many homozygotes are certainly easily modified by selection I feel under no obligation to claim that heterozygotes are modified more easily.

At all events it is not this point which led Wright to deny the efficacy of the selection of modifiers, but the purely statistical confusion of arguing that other selective actions to which these same modifiers may be subject could retard selection for dominance modification in bringing about its effects.

I am sorry to have to trouble you with this long letter, but sometimes a personal explanation does help towards the avoidance of confusion in the literature. I should, of course, be heartily glad if you found it

possible some time to correct the false impression which you have given of my views, and which, as you will be the first to understand, is bound to cause a deal of vexation. In reading your summary I find myself agreeing with every work except the last, and that only because I had regarded the theory of dominance as contributing materially, and from a new angle, towards demonstrating the other propositions you have stated.

Yours sincerely,