

JULY  
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Dear Major Darwin.

I will answer your letter in spite of your protest, because you are one of the very few people who will ever appreciate the consequences of my suggestion; so I shall be especially particular that you shall understand me clearly about its framework.

I take O and M to be physical organic structures (genes) handed on from generation to generation. For some millions of generations selection has always favoured O and we should have long ago seen the last of M if O had not regularly mutated or changed into M, sufficiently often for about one in a million O genes turn to M in each generation. This keeps a certain supply of M in being, a number proportional to the mutation rate, though also influenced by the intensity of the counterselection.

If M possessed an advantage over O, no such situation would have occurred for M would replace O, apart from back mutation, in a few thousand generations. [I need to think about the case in which M is sometimes, in certain places advantageous]. The case I deal with, and to which I believe the mutations of our little genetical samples nearly always belong, are the unfortunate failures.

If the mutations of O were of several different kinds, producing M, M', M'', etc., (as is known in some case to be the

case,) from the same kind of O, this will not help any progressive change, for the mutants we deal with are those which ~~are~~ actually arise in the cultures and are brand new; in any case the old mutant genes must all fairly soon be extinct, the supply depending upon fresh mutations occurring. However, something does seem to have ~~happened~~ happened to O, supposing it to have been originally a mutant of a proto-original gene, W, for, whereas the heterozygotes OM, OM', OM'', all look like O, the heterozygotes which we build up by artificial matings MM' etc., are intermediate between MM and M'M'. This is my first fact; the original puzzle which set me thinking. For even when M' arises as a mutation from M, MM' is still intermediate.

Your more dominant form  $O^+$ , I represent by  $Oa_1$ , and the less dominant form  $O^-$  by  $Oa_2$ ; here  $a_1$  and  $a_2$  are alternative genes, one of which doubtless arose from the other by mutation. There may be any number of such so called modifiers (all mendelian factors are modifiers if we choose to think of them as such, though doubtless some only affect the degree of dominance shown in OM); thus  $Oa_1b_1$  may be  $O^{++}$

$$\begin{array}{l} Oa_1b_1 \text{ may be } O^+ \\ Oa_2b_1 \text{ " " } O^- \\ Oa_2b_2 \text{ " " } O^{--} \end{array}$$

All that this means is that  $OMa_1b_1$  is most like O,  $OMa_2b_1$  most like M,  $OMa_2b_2$  least like O) and the other two intermediate.

Quantitatively, the effect of the modifying factors on MM, if any, is of no consequence, so long as dominance is incomplete, for MM will be then so exceedingly rare that no appreciable

part of the ancestry of existing individuals will <sup>have been</sup> ~~be~~ MM. But I show that an appreciable part will often be heterozygous, OM, and in this part the + modifying genes will have been selected, thus tending constantly to produce complete dominance.

It is interesting that such a selective influence acting on a thousandth part of our ancestry should have made us completely dominant to the many unfortunate mutants which have been shot at our race, and this ~~xxxxxxxx~~ accords with the view that they have been clamouring at the gates for more like millions than thousands of generations.

Since we distinguish the effects of the factors *a*, *b* etc., only in the combination OM they cover both the distinctions of your latter  $O^+$  or  $O^-$  and  $M^+$  and  $M^-$ .

About the supply of modifiers there is a very satisfactory answer. If I wanted to increase human stature I should select from the mass of modifiers in the existing population, and quickly enough build up a type exceeding the tallest normal variants. At this stage I should expect physiological disharmonies to appear. (contrast <sup>of</sup> growth, blood pressure etc) and selection would be chiefly concerned in remedying these, and if the process had only taken 10 generations or so, I might be held up and have to wait for favourable mutants; but if I were content to produce the same change by a mild selection in 10,000 generations, I could never deplete the supply of modificatory variance, and it would always be available well in advance, as it is now in stature. In modifying ~~the~~ dominance natural selection only examines one individual

in 1,000 or 10,000, and consequently the supply of modifiers is never depleted, and the minute selection at work produces always its full effect!

But what a striking effect for such a minute selection!

Yours sincerely,

W. G. L. A. F.

Eldon Moore has gone for Pearl in the July 'Review'. Rather well I think.