Fisher to A.B.D. Fortuyn: 20 April 1931

It was a great pleasure to me to receive your kind letter about my book on Natural Selection. Its publication has been too recent for me to be able to judge with any confidence of its effects on scientific opinion generally, and it is therefore of particular interest to me to receive your personal impression.

I had read Dr Hagedoorn's stimulating book[38] some years ago, at a time, however, when my own views as to the bearing of genetics upon evolutionary theory were quite immature, and my reaction was, therefore, probably less favourable than it ought to have been. Professor Sewall Wright of Chicago, an extremely able geneticist, who on most points has given me extremely valuable support is, however, powerfully advocating the importance of partial isolation as an evolutionary factor, and this, I believe, was one of Dr Hagedoorn's principal contentions.

I think we must distinguish sharply between the processes causing evolutionary modification and those causing fission or subdivision into distinct species. The term 'origin of species' may be used in either sense. As far as I can see at present, isolation, whether geographical or physiological, while of immense importance to the problem of fission, is not a primary factor in adaptive modification, save in the subordinate sense that fission is a necessary condition for divergent adaptation. Sewall Wright, however, at present thinks otherwise, and there are very few men who have a better right to form their own opinion.

I was particularly interested in what you say with respect to the argument in the chapters on Man. This argument had to be developed rather fully, since, unlike the other applications of selection theory, such as sexual selection and mimicry, there is, as yet, no considerable literature on the subject. I would be especially interested to hear if you have formed any opinions, during your stay in China,[39] as to the temperamental contrasts between the anciently civilized Chinese and either Europeans or the less civilized nations of N.E. Asia. Such temperamental contrasts are, I believe, of the highest importance in human evolution, and, though the difficulties of setting one's impressions upon an objective basis are very great, yet I am convinced that a sympathetic observer who faces these difficulties can accumulate results of permanent value, and of very widespread interest.

Fisher to A.B.D. Fortuyn: 13 January 1939

Thanks for your long and interesting letter. I do not know whether what I have to say on your points will be particularly helpful, but at least it should serve to make clear my own point of view. With respect to your citation from *Statistical Methods*,[40] I certainly want you to understand what I am driving at. In England, at all events, and to a fair extent elsewhere, the cleavage in opinion between statistical and genetical studies of inheritance had been drastic and injurious. For twenty years I have laboured, with more or less success, to get statisticians to appreciate the importance of Mendelian inheritance, and to get geneticists to appreciate statistical methods. The phrases you quote are in the latter category. You ask if it is wise to support in this way a rather too simple popular idea. The simple popular idea which I am opposing, however, may be made clear. It is that familial resemblance may easily be ascribed to differences in the social and economic conditions of different families, and that inheritance should only be postulated where genetical factors have been individually analysed and recognized. This attitude seems to be widespread, and is, I believe, profoundly untrue. On the other hand, I know of no work pointing to any measurable factors capable of explaining quantitatively more than a very small fraction of the observed covariance in the resemblance between relatives. I infer that this is predominantly due to similarity of inheritance involving many factors.

I appreciate your point that inheritance is often strikingly demonstrated by the differences, especially in characters which can be appreciated but not measured, observable between brothers and sisters, whose social and economic environment has been certainly very similar.

Of course, the more factors you introduce, the more seldom will genotypic identity occur, even between near relatives. On the other hand, the more frequently will similar, but not identical, genotypes be phenotypically indistinguishable, so that in a multiple factor system you may expect a measurable degree of similarity between parent and offspring, and between other near relatives. ...

Fisher to A.B.D. Fortuyn: 11 December 1944

I was very glad to receive your letter. ...

I hope you were interested in the response to selection of the tail-development with Danforth's mutation [*CP* 199]. It seems to show that the stocks I had in England, though comparatively inbred, were really (though invisibly) highly heterogeneous for factors which, in the presence of the short-tail mutation, are capable of influencing the development of the tail. It is this great pool of latent variability which I think geneticists of the period of the rediscovery of Mendel's work at the beginning of the Century very greatly failed to appreciate. ...

Fisher to P. F. Fyson: 5 September 1938

Thank you for your letter of August 21st, which I have just received on my return from holiday. You have my entire support in the belief that the [Eugenics] Society ought to take a much more active interest in current politics and should throw its weight more strongly in favour of positive measures. For years, indeed, I have felt that the controlling group in the Society were almost without Eugenic knowledge or ideas.

I am not so sure that the decline of civilization should be ascribed to licentiousness, though, obviously, this does a great deal of harm personally, just as does drunkenness, yet my impression is that Gobineau was right when he asserted, in the early paragraphs of his essay on the inequality of man, that the early and virile stages of successive civilizations were not more exempt from licentiousness than were the later and decadent phases. I should say, indeed, that self-control in general tends to increase in the history of all civilized peoples, even while their capacity for spontaneous co-operation and the pursuit of unselfish aims is diminishing. I think, however, you would be right to point to moral laxity as an important symptom of social disintegration.

Fisher to P.F. Fyson: 12 September 1938

Thanks for your letter. I do not see that much can be done with the Eugenics Society, as its present directors of policy are strongly entrenched and appear almost impervious to scientific advice. Indeed, I think they are suspicious and resentful of it. In consequence, I have of recent years not attended the Council, although I have allowed my name to remain as Vice-President.

Fisher to R.R. Gates: 1 July 1930

... With respect to blood groups,[41] I fancy we must give up the two factors in favour of a multiple allelomorph series, **O**, **A**, **A′**, **B**. They seem to resemble *Apotettix* in their dominance, i.e. there is a fairly common universal recessive, and a number of dominants, which however show no mutual dominance, but a combination of the single effects. I cannot think what such a factor is doing in Man.

There are a good many climatically limited blood diseases, such as malaria and yellow fever, so I would not be too sure of the absence of selection. However, if it is absent, a mutation rate of 10^{-6} will establish itself in about 62 per cent of the population in 10^6 generations, which seems too long to allow, or a little less than 10 per cent in 10^5 generations, which is still a long time, and an uncomfortably low percentage. It looks as though you must postulate high mutation rates ethnographically limited, or else local selection.

Fisher to H.D. Goodale: 2 January 1932

I think I can make somewhat clearer that part of my letter which you find questionable, for I have evidently not expressed myself very clearly. I entirely agree with the principles you lay down:—

(1) the rating given to a bull should be based on the information supplied by the performance of his daughters and their dams,

(2) convenience and genetical common sense agree in suggesting that the appropriate type of formula is found by taking some multiple of the daughter's yield, and deducting some (other) multiple of the dams' yield. Thus our estimate from a single heifer would be:

$$aH - bD$$

where H and D stand for the performance of heifer and dam, and a and b for the constants of the formula.

In an extensive paper for which, I believe, Gowen did the calculations, Pearl tabulated the mean values of

$$H - D \tag{1}$$

for a large group of bulls. Examining the groups of bulls which stand highest and lowest on his list it is obvious that those that stand highest had been mated to exceptionally poor cows, and those that stand lowest to exceptionally good cows. The formula in fact gives too much weight to the dam and too little to the heifer. Since half the germ plasm of the heifer comes from the bull, the formula

$$2H - D \tag{2}$$

suggests itself as more plausible, i.e. free from gross error, though probably capable of improvement. To this it has been objected (by Lush) that if we consider the different daughters as giving different estimates of the rating of the same bull, (2) will be more variable than (1), and consequently must be judged less precise. This criticism overlooks the fact that using (2) the ratings of the different bulls will also be more widely spaced, so that their differences will be as significant as before in relation to their higher standard errors. The inadequacy of considering only the variance of different estimates of the same bull may be easily seen by considering the formula

$$H - \tfrac{1}{2}D \tag{3}$$

which is obviously equivalent to (2), but gives a lower instead of a higher variance for different ratings of the same bull.

It is for this reason that I introduce the condition that the variance of the different ratings of the same bull should be minimized in relation to the variance of the average ratings of different bulls on the same formula. Applied in this way we are only concerned with the ratio b/a, and it is obvious that it is only this ratio which matters in the application of the formula.

To take the variance among different bulls as the denominator of the fraction to be minimized does not imply that a different formula would be obtained if this variance is changed. If the true ratio of b/a is the same, we should obtain estimates of it, agreeing within their sampling errors, from groups of data having very different variabilities of the bulls tested.

We should, I think, however, recognize that the ratio must depend on the particular group of genes segregating in the material examined, and on the degree of inbreeding, so that it may really be different in different lots of material. If this is so, it will be a real advantage to apply to each group, the formula appropriate to its peculiarities, instead of a single formula for all cases. ...

Fisher to J.B.S. Haldane: 15 March 1930

I think you may like to see the enclosed [*CP* 87] which I have written but not yet decided to publish. I should much rather wait a year or two for fuller information; in fact the only case for publishing at once is that it may speed up the further investigations which are needed.

If any points occur to you please annotate the copy freely. It is not, of course, primarily an answer to your note, but a further development of my own theory on lines suggested by your note, and especially by your suggestion of duplication.

Let me have it back soon.

J.B.S. Haldane to Fisher: [March 1930]

I have read your typescript with great interest ...; here is my serious criticism. Nabours has since published a big paper (*Bibliographia Genetica*, V). ... I feel that any discussion which does not include these data is premature.

However, the theory, especially as regards *Lebistes*, is most attractive, and I like the idea of an evolving species doing one thing at a time. I am glad my note has stirred up thought on the matter. I agree that my suggested limitation is 'curious', and that your criticism of it is quite cogent. That is a fair tit for my tat as to the, to my mind, 'curious' specificity of your postulated modifiers. I feel, however, that all this back-chat is leading somewhere. I hope you will publish after digesting Nabours' new data. ...

I have not annotated because I feel you may modify in response to Nabours' new stuff. If so, perhaps I can see the paper again. I am just doing the theory of segregation in polyploids, also monstrous calculation on inbreeding with 22 simultaneous difference equations, which admit of a simple solution.

Fisher to J.B.S. Haldane: 25 March 1930

I had looked through the *Bibliographia Genetica* material, but unfortunately it cannot be used for examining the viability of the dominants, since the zygotes are not recorded. For example, you suggest in your letter that the matings showing segregation in $\times/+$ were all matings $\times/+ \times +/+$, and these I could use readily. But Nabours refers to his 1917 paper for an example showing the segregation of **C/9** and the mating was actually **C/9** $\times$ **B/E** giving four types all heterozygous.

Possibly on seeing my paper he will sort out the evidence for other species, and I should be especially pleased if on large numbers there should be no significant deficiency of $+/+$. On this point my paper only raises a question which cannot be answered for the data published so far.

I am glad you like the beneficial mutations all having to 'cue up' (or is it 'queue up'?) when linkage is too tight.[42] Let me have any further comments soon as I am being urged to publish.

J.B.S. Haldane to Fisher: 29 April 1930

Referring to your esteemed favour of 23rd inst.,[43] you suggest two alternatives: (a) that the liability to respond by agglutination to any particular ingredient in the serum is always completely dominant; (b) the liability of recessives so to respond is always shared by the heterozygotes. I do not see that (b) has a definite meaning; to my mind the definition of a recessive is a zygote having a character *not* shared by the heterozygote.

With regard to the suggestions, Todd has not, so far as he knows, got any homozygotes. I have had a look at some of his results, and he is trying to get some, only choosing what would appear to be fairly recessive birds to mate together, as these would seem more likely to give a pure line within a measurable period.

Perhaps I have not got your point, however. I should expect to find both dominance and summation of effects, as with the human blood group genes, where **AO** is indistinguishable from **A** (**A** dominant) and **AB** differs from **AA** or **BB** (no dominance).

With reference to your book, I have finished the first reading, and think the suggestions as to 'inertia' on pp. 111, 137 [*GTNS*, pp. 125, 152], and elsewhere, are even more important than the theorem of p. 35 [*GTNS*, p. 37], as they may serve to explain a good deal of otherwise unintelligible 'orthogenesis'.

I disagree with the statement (p. 119) [*GTNS*, p. 133] that linkage values are eminently susceptible to selective modification. Linkage modification is generally due to cytological change (segmental inversion) and in this case intense linkage is characteristic of cytological heterozygotes, not of pure lines save for the genes concerned. Also I doubt if linkage will be much affected by selection if the COV [cross-over value] is large compared with the coefficient of selection *m*.

The social part is highly controversial. If you convince me I shall have to become an extreme form of socialist, since the inheritance of property must tend to promote infertile stocks, even with family allowances of 12% on income per child. E.g. if I have one child and an income of £1120, while you have 6 and an income of £1720 you may save more than I, but you are not likely to save 6 times as much. So your children will start with less capital than mine. I suspect your economic views represent a compromise between the conclusions of your probably unorthodox but 'bourgeois' economics, and your non-bourgeois (—non-proletarian either, but shall we say human—) biology.

Correct me if I am wrong. I have not yet begun to digest the book, especially not pp. 106-110 [*GTNS*, pp. 120-4].

Fisher to J.B.S. Haldane: 29 April 1930

Many thanks for your letter; you can scarcely guess what a satisfaction it is that my book has found at least one very intelligent reader. I kept feeling all the time 'This won't be understood unless I expand it to a whole chapter about things I really know nothing about'. It is tremendously good to feel that you are reading it carefully, and I hope you will write again as the spirit moves you on any points you care to discuss.

One thing which makes me think that linkage values would respond readily to selection is the appreciable discrepancies between the linkage values in different lines of *Drosophila*. I do not mean large scale suppressions which, like you, I should put down to segmental inversions, etc., but the general heterogeneity of all extensive data which makes linkage maps always relative to a 'standard stock'.

I do not believe (if I convince you on Man) that you will be attracted by any existing 'ism'. I only fear that you will say that it is so intricate that we must cut the Gordian knot by ectogenesis. I may be wrong about inherited capital, but I do not believe it is important in a sufficiently large class to be a major factor in the problem; though I do think that if family allowances were general among earners it would seem normal and natural (and on racial grounds desirable) to consider national insurance schemes applicable even to millionaires, which would have the effect needed. But, again, I am convinced that it is the body of the population that matters, not the economic extremes. Your point about capital *saved* out of earnings really means, does it not, that somewhat more than 12% would be needed to equalize the standard of living.

I realized in our talk last week about two factors that 'maintain each other mutually in equilibrium' was a misleading phrase in suggesting that pairs of factors could be held in equilibrium by an agency essentially different from the case of one factor. All that I meant was that cases of stable equilibrium in two factors can occur for which the one factor analysis was inadequate and that all such cases must favour close linkage, as the single factor cases favour cross-fertilization. Possibly the case on pp. 110-11 [*GTNS*, pp. 124-5] is the more important agency of this kind, but I do not think there is any agency of the same sort favouring looser linkage, which may give us a gauge ultimately for W.

Wherein are my economics bourgeois? Are you thinking of pp. 182-4 [*GTNS*, pp. 201-3], or is it merely that I do not go out [of] the way to consider a collectivist egalitarianism which has never existed?

As a biochemist, have you any preference as between the diagrams on pp. 63 and 64, [*GTNS*, pp. 70-1]?

About agglutination you are right; (b) means no dominance in that matter, though a dominant genetic factor like Barred might show no dominance in its serological reactions. I take it Todd using Plymouth Rocks has homozygotes for a fair number of factors, though his stuff shows plenty of variation in other factors which do not affect the plumage. I want to know if he could make up particular brews which would discriminate sex, or any other known genetic factor *alone*. When you see my meaning about this I expect you will be able to say how the test could best be made, and I hope you will if Todd is interested.

Fisher to J.B.S. Haldane: 14 May 1930

I have put some notes on the margins of your 'Further note on dominance', but they may be only criticisms of your wording. It would, I think, be a really good point if multiple allelomorph series had a number of recessives on one side and semi-dominants on the other, but the case of the rabbit is not easily reconcilable with any simple response curve. If the 'dominants' are dominant through producing more effect than the normal, all the recessives ought to be incompletely recessive, through the reduction of the effect in the heterozygote, i.e. they ought to appear semi-dominant also. If you build up a response curve to fit the facts of dominance it needs almost as many inflexions as there are allelomorphs. ...

J.B.S. Haldane to Fisher: 6 June 1930

I do not altogether agree on the necessity for inflexions in the (gene stimulus) - response curve. Suppose that x represents amount of gene substance (i.e. something additive as regards genes), and y the effect measured. Then $y = f(x)$. Supposing $y = k \log x$ (Weber's law), then it is a sufficient condition for dominance that the minimum distinguishable change in y should exceed $k \log 2$. Thus a gene of value a will be dominant over one of value b if $a > 3b$

	Gene value x	Phenotypic value y	Difference
Dominant	$2a$	$k(\log a + \log 2)$	
			$k \log 2 - k \log(1 + b/a)$
Heterozygote	$a + b$	$k \log(a + b)$	
			$k \log(1 + a/b) - k \log 2$
Recessive	$2b$	$k(\log b + \log 2)$	

Clearly the first difference $< k \log 2$, the second $> k \log 2$. ...

P.S. I am reviewing you for the *Eugenics Review*.

Fisher to J.B.S. Haldane: 10 June 1930

... The argument involving the 'minimum distinguishable change' is worthy of the High Court of Justice, but is experimentally at the mercy of anyone who, by observing more animals, or under more comparable conditions, takes the trouble to distinguish smaller changes. Of course, its consequences might be verified by such an observer.

'Bourgeois' economics still puzzles me. The word is really rather well defined, so I suppose you did not mean just reactionary, or did you? That would be true if the reaction is taken to be not merely to the progressive party's programme but to the whole interaction of the two antagonistic politico-economic principles. They play into each other's hands in guaranteeing the process of Chapter XI, but by doing so thoroughly frustrate each other's aims. ...

About Todd, he seems to think you have some reason against sex being distinguishable by his method, but if you thought it worth doing I believe he would make the following test for the ♀ chromosome:— Make a compound serum from cocks using hen donors; exhaust with corpuscles from several cocks; try if it reacts to hens. If it worked, it would be a good first step towards detecting a single gene.

I am rather sorry about the *Eugenics Review*, as I had hoped you would be collared for *Nature*, but perhaps you will do both. At any rate, the *Review* will give you all the space you want.

J.B.S. Haldane to Fisher: 9 November 1930

I enclose a draft of a paper on selection as a function of mortality rate.[44] The conclusions are rather odd, but I cannot get away from them. They remain true for small values of mortality even if the viability distribution ceases to be normal for large deviations (as with human stature). If you see any *gross* error, will you let me know as soon as possible ...

Fisher to J.B.S. Haldane: 11 November 1930

I think I see the point of your calculations now. I should take $+ \log (z + 1)$ instead of $\log z$, since $\log (z + 1)$ measures the amount of elimination in the sense that if such a process, e.g. decimation, is repeated, $\log (z + 1)$ is doubled. ...

I do not think one ought to be surprised at the result that small mortalities are much more efficient selective agents, in that they produce a greater effect 'per decimation'. One would find very much the same taking the variate selected as an ordinary heritable variate, and not confining the heritable difference to two groups having different means. Actually, I suspect that selection always acts by a graded series of rates of death or reproduction, rather than by truncating the distribution. ...

Fisher to J.B.S. Haldane: 17 December 1930

Many thanks for your note ....

When I found that, contrary to my anticipation, you were not reviewing my book in the *Eugenics Review*, I feared that there might have been some muddle, but my enquiries from Cutler and Major Darwin both showed that they thought that nothing of the kind had occurred. I have since learnt that you had been willing to write a review, and had possibly even written one, and I am exceedingly sorry that for some reason it has never appeared.

I still think a review from you would be most valuable, and this even apart from my personal interest in how far you are willing to go with me, especially on the human part, which has not in the English reviews been given very much space. I do not think they are wrong scientifically in stressing the purely biological parts for these constitute the scientific foundation of the rest, but the human inferences, if well founded, are of such practical importance that they will certainly be the ultimate centre of interest.

Is it too late for you to consider whether it would not be worth while to allow what you have written, or what you would like to write, to appear in the *Eugenics Review*? I understand that the Editor would be very glad to have it, and I should very much regret it if you of all people contributed not one of the notices of the first edition.

Fisher to J.B.S. Haldane: 6 February 1931

I am sorry that the M.S. has disappeared.[45] I should greatly have liked to read it. What do you think, though, of putting down something on Man in particular, since a great deal of what I have written, believing it to be a single and coherent argument, has never been criticized, and therefore presumably not followed. The diagnosis of the differential birth-rate is central, and a great deal both of theory and of practice must hang on the diagnosis chosen.

J.B.S. Haldane to Fisher: [*March 1931*]

... I think it would be an excellent thing to present your results about eugenics in a more popular form. I hope you will refer to the fact that Berlin, as well as Stockholm, has now got a net differential fertility in favour of the rich. However, I take it the Malthusian parameter for *all* classes is negative.

Fisher to J.B.S. Haldane: 17 March 1931

... Do you believe the Berlin tale? The fallacies of Edin's work on Stockholm[46] are fairly easy to see, but I have not looked at the Berlin stuff.

Fisher to J.B.S. Haldane: 1 May 1931

Many thanks for the M.S. you have turned up at last.[47] I have sent it on to Moore. Naturally I find it extremely interesting, apart from its flattering aspect. I agree with you entirely that the main scientific point is to test very thoroughly the theory that social promotion is the main cause of differential reproduction. But the main practical point is to combat the idea that racial decay, or the differential birth-rate, or any other social phenomenon which we judge undesirable, is to be accepted fatalistically as the 'Will of Allah', rather than tackled scientifically like *rabies.*

Fisher to J.B.S. Haldane: 24 May 1933

As you will already know, I have been invited by the special board and by the Provost to apply for the Galton professorship,[48] and shall do so as soon as I can find the Registrar's letter on the subject. The situation is peculiar, but interesting, and I ought to thank you first for the great part that you have undoubtedly played in putting the invitation in my way. Apart from snails, which I think I can keep anywhere—and poultry, alas! nowhere, unless I can keep them on at Rothamsted, there appears to be an 'Animal house' equipped for the nurture of putrid little dogs, which should do for mice, though the rent and maintenance charge of £345 seems a little extravagant for the purpose. So if you have an overflow of rabbits or kangaroos or anything from your department I should do my very best to make them welcome. I hope you won't hesitate to convenience yourself in this way, especially as some day I might want you to wangle me a little Naboth's vineyard down at Merton.[49] Besides I think that this sort of hospitality is extremely valuable in giving members of different departments a chance of knowing something about what is done elsewhere, provided, of course, that their chiefs are not fighting about tithes of mint and cummin.

The great problem seems to be to get anything like personal assistance. I find that the lecturer in medical statistics in the department (or perhaps now it will have to be Medical Eugenics) has a whole time research assistant at his disposal, whereas the Professor seems to have a secretary up to £150 a year who may not be versatile enough to feed snails and work a calculating machine when she is not typing letters. My best hope seems to lie in the allocations for the wages of the dog-man, and especially for their food; I have great hopes of their food.

Tell me, who knows next to nothing about University organization, supposing mathematically trained lads come to me, hoping to get some sort of a doctorate by working in my department, knowing nothing, and not very willing to know anything of experimentation with living material, can I make them attend lectures in your department on genetical theory as, at any rate, one step towards apprehending the kinds of reasoning used by experimenters? And will they have any reason to believe that the knowledge so acquired will help to make their theses acceptable? Perhaps the right way is to get a geneticist appointed as outside examiner, but does the Professor choose the outside examiner? *Per contra,* will you want me to chat of co~~n~~variance to babes of yours?

But instead of my writing at random, tell me when I can meet you and hear what you have been thinking about it.

J.B.S. Haldane to Fisher: 30 May [1933]

Please do not thank me in connection with your appointment. When asked my advice I mentioned a number of arguments against you, some of which were new to members of the committee. It was the merest regard for truth, and not any personal regard which I may feel for you, which forced me to add that you were the only possible candidate for the post.

There should be absolutely no difficulty about co-operation between our Departments. ... I shall be very glad to talk any details over with you any time ...

J.B.S. Haldane to Fisher: 23 March 1939

I hope to have the paper leading to the calculations of the value of α ready in about a week. I think the most interesting point in this paper[50] is that it clears up the reason why human recessives are so scarce. I never believed Levit's theory,[51] which is held by various other Marxists, that natural selection is more or less inoperative in man, any more than I believed in yours as to its social determination at the present moment.

I should be genuinely interested to know if you think there is a way round the argument developed in this paper—given that the mean coefficients of inbreeding are substantially correct, of which I have little doubt.

J.B.S. Haldane to Fisher: 25 June 1940

I enclose a note for the *Annals.*[52] ... It is fairly clear that where you have parental or sib correlations of the order of 0.8 for the age of onset of a disease you cannot be dealing with modifiers, but several different genes must be concerned. Almost all the variance is between pedigrees and not within them. It looks as if your views regarding modifiers were correct for Huntington's chorea and optic atrophy, while in Friedreich's ataxia, for example, they play a minor part. ...

Fisher to J.B.S. Haldane: 27 June 1940

Thanks for your note for the *Annals.* ...

I am a little puzzled to know what you mean by 'It looks as if your views regarding modifiers were correct for Huntington's chorea ...', as I do not take any objection to the notion of multiple allelomorphs in rare defects. ...

I think your discussion of the causes of variation in age of incidence in families is really valuable.

J.B.S. Haldane to Fisher: [*September 1940*]

Can you help me on the following question? In a series of estimations of blood constituents, the mice of genotype **A** were compared with those of genotype **B**. The means of the two groups differ nearly significantly ($P =$ 0.07). But there seems to be a decided correlation between litter mates. If we had only one per litter of each genotype we could simply find the mean of the differences. In the data enclosed I have calculated t from the differences, giving the mice in the order of their occurrence in a table of Grüneberg's. This is illegitimate. I have also averaged each genotype. Finally I have averaged litter mates. This sacrifices some information, but seems the best method.

Is there any simple method of dealing with such a case? If so, is it published? Such cases are likely to occur with increasing frequency. I cannot find them treated in your 7th edition of *Statistical Methods.*

This place[53] has been heavily bombed. The Great Hall and Physical Laboratory are wiped out. The library has been partly burned and partly flooded. We are still carrying on, as we have nowhere to go. Do you know of any possible refuge? We only need electric lights, a wash basin, gas, and a little (very little) artificial heat.

Fisher to J.B.S. Haldane: 26 September 1940

Thanks for your note. As an emergency measure what do you think of coming down here?[54] I am entitled, without more ado, to add one to the number working in the Department, and with some ado it should be possible to get Sir John Russell, the Director here, to consent to arrangements for your assistants. Are there two at the moment?

We get daily warnings here, but no raids so far. Russell takes the reasonable view that we need not obligatorily cease work on a warning, but should place ourselves to avoid flying glass, and take cover when there is actual firing, or near bombing. Conditions for work will not be ideal, but perhaps no worse than any obvious alternative. I should be delighted if you found this possibility one you could utilize.

Your mouse problem is just the beastly sort of thing you would dig up. I mean that it involves two distinct estimates of error, between and within litters, unless you can get both genotypes in the same litter. If you can, which I can't verify from your rough sheets, then a decent test can be worked using only variation within the same litter.

Fisher to S.C. Harland: 11 October 1940

Many thanks for your letter, which I am very glad to get. Nothing could be jollier than a situation in which scientific views were discussed with the exactitude and impartiality appropriate to pure logic, for in that case any new fact is an obvious enrichment of the material available to all thinkers, and a new argument is as good as a new tool in a workshop. We should perhaps feel grateful and gratified all round; but in fact the situation of research is rather different. Actually, almost anyone who makes a scientific advance of almost any kind is bound to be exposing, as erroneous or obsolete, views and methods formerly taught and trusted. The teacher especially who is accustomed to pontificate is decidedly reluctant to eat his words or to recast his courses. He therefore finds some excuse for not doing so by ignoring or, failing that, belittling and criticizing, with more or less astuteness, views which threaten his current stock of ideas. This temperamental factor is almost always in evidence in the earlier reactions to any new notion, and of course the publication of new findings and the discussion of their relevance is not really carried out in logical terms, much of what is said being read, and I suppose written, in the sense of a vote *Aye* or *No.*

In fact, of course, controversy even with ruffled tempers does not do nearly so much harm as might be expected, but it does enough harm to make me want always to avoid writing severely except in cases where unfair personal attacks have been made on a third person.

On the question of modifying factors selected on their own account, there is a distinction worth making, of which I do not know whether you have ever formulated it to yourself: it is exceedingly difficult for any factor to be mathematically neutral; indeed this is almost impossible, but even to be neutral enough for the incidence of such factors in a large population to be approximately as though they were neutral requires a balance of forces about as accurate as a chemist uses in the finest chemical weighings. Consequently, the factors actually used in dominance modification will necessarily be predominantly those which have some, perhaps slight, selective advantage on their own account. This, however, affords no explanation as to why dominance is modified in the right direction; the explanation lies in the additional selective advantage afforded by improvement in the heterozygotes, i.e. there is no need to postulate that those genes which make changes of dominance in the right direction do *ipso facto* enjoy any selective advantage other than that provided by the improved viability of the heterozygote.

This is presumably true of all selective effects without exception, e.g. those by which the spur of a cock was built up were presumably the most advantageous, or least disadvantageous, of those by which the same morphological change could have been brought about. ...

Fisher to H.W. Heckstall-Smith: 23 January 1957

Thank you for your pamphlet[55] and your letter of the 22nd. So far as I can see, controversy will be confined to matters of proportion, for those are very important in exciting anxieties. My own view is that damage to life, health, and property are far more important effects of atomic weapons than damage to posterity through injuries to the germ plasm, though the latter rouses the most acute anxiety to our instinctive feelings.

With respect to the latter I am inclined to discountenance exaggeration largely because the future germ plasm of the human race seems to me threatened by so much graver danger from other causes, and that stress upon the rather hypothetical damage to be feared from nuclear warfare is likely to obscure, and may even in some cases be intended to obscure, the measures we ought to take to protect future generations from these other sources of injury.

Fisher to L.T. Hogben: 6 May 1932

I am not now working on the problem you mention,[56] so please go ahead without scruples. What originally made me ignore the sex-linked case was the absence of any apparent effect in the old Pearson and Lee Father-son, Father-daughter, Mother-son, Mother-daughter correlations.

The work for these was all done about 30 years ago, and the Biometric Laboratory has never confirmed the results from independent material. This might well be worth doing. The School Medical Officers' height measurements would, after correction for age, give many thousands of the 3 sorts of pairs of sibs, which might well give an idea of the importance of the X chromosomes in human heredity (assuming the Y chromosome is of no importance, which in view of the Hapsburg lip one scarcely likes to do).

I do not think the sex-linked case especially suitable for selection, and think you altogether underestimate the efficiency of the latter. After all, quite moderate selection is known on biometrical grounds to alter the mean stature by 1 inch in a generation, say a foot in 400 years. That [the] human population has not changed at this rate is evidently due to the character not being strongly selected.

Fisher to L.T. Hogben: 25 February 1933

I think I see your point now. You are on the question of non-linear interaction of environment and heredity.[57] The analysis of variance and covariance is only a quadratic analysis and as such only considers additive effects. Academically one could proceed in theory, though in a theory not yet developed, to corresponding analyses of the third and higher degrees. Practically it would be very difficult to find a case for which this would be of the least use, as exceptional types of interaction are best treated on their merits, and many become additive or so nearly so as to cause no trouble when you choose a more appropriate metric. ... However, perhaps the main point is that you are under no obligation to analyse variance into parts if it does not come apart easily, and its unwillingness to do so naturally indicates that one's line of approach is not very fruitful.

Fisher to Aldous Huxley: 23 September 1931

I have collected three excuses for writing to you, (i) that I think you know my name already, (ii) that I have been for some years very good friends with your brother, the biologist, and (iii) that I am at present on my back regenerating discarded tissue and have been reading an old book of essays of yours, *On the Margin*,[58] with very great satisfaction.

What a remarkable series of changes you call attention to in the one on 'Accidie', and what a good example of the change demonstrable from literary sources of the habitual attitude of mind towards the same experience. I had noticed the contrast between the gracious young lady called Ydelnesse in the 'Romaunt of the Rose' and her namesake riding the ass in Spencer, but I had not at all appreciated the 'subtle and complicated' vice you describe. It is really delightful the way this melancholy sulkiness changes from a vice to a disease as the machinery of social co-operation changes from the excitation of common emotions to the pursuit of individual interests. The melancholy man who does not share your hopes and lively intentions must seem as much a traitor to all decency and right thinking as a little brother or sister who unexpectedly expresses a distaste for some gleefully anticipated game. Could one's anger at such a disappointment be other than a *moral* indignation? And I suspect that for the greater part of man's social history he has relied far more on the infectiousness of emotion than on expressed or implied contracts, for getting people to work together.

Of course, the mood only becomes a sin when it is already taken for granted that social co-operation is a binding obligation. It was not a sin in Achilles, though I suppose it would have been in a crusader taking similar umbrage. What makes it specially valuable is that the Middle Ages is just that section of our history which is most difficult to parallel in other civilizations. I suppose Accidie must have been a sin some time between Homer and Solon, but one could scarcely hope for evidence of it, and the 'Middle Ages' of the Islamic civilization were telescoped into a couple of generations under the Ommayads.

Was the later literary affectation principally attractive as an *Aristocratic* contrast to the jauntiness of prosperous mediocrity, or by the fatal allurement of a malady curable, perhaps, by sympathy and feminine graces? You notice that I reject your theory that we have a right to our Accidie.

Has anyone taken you to task for your injustice in Cardinal Maury? (p. 123). Your exclamation recalled a sentence of Gibbon: 'And, since mankind must be either compelled or persuaded to obey, the use and reputation of oratory among the ancient Arabs is the clearest evidence of public freedom.'

See how argumentative it makes one for his chief work to be, like mine, purely vegetative. Don't bother to answer unless I've recalled a vein that amuses you.

Aldous Huxley to Fisher: 26 September 1931

Thank you for your very interesting letter. I think your diagnosis is quite right and that the sinfulness of accidie was stressed at the time when individuality was breaking out of social co-operation in what must have seemed a most dangerous way. Like heresy, it was punished for being anti-social. I shall put your suggestion up to Gerald Heard, who has written so curiously and learnedly on just this question of the rise of individuality in his *Ascent of Humanity* and *Social Substance of Religion.* Once the individual has been completely separated out and is aware of his separateness, accidie, I think, becomes inevitable among those who have too much leisure. Certainly the aristocratic motif entered in at the Byronic period. Being able to afford boredom was—and I suppose still is—very distinguished. Finally there is the type of boredom illustrated by those unhappy South Sea Islanders described by Rivers—dying of ennui because we have killed the old religious purposefulness in their life and substituted mere distractions. This kind of boredom occurs nearer home; the total laicization of modern amusements, the fact that they exist only for their own sake and not with some ulterior aim in view—such as would be the celebration of some event in a communally accepted religion—this robs our 'good times' of much of their efficacity. The moment the distractions cease, boredom is apt to set in. Hence the 'continuous performance' of our movies.

No, perhaps we have no right to boredom. But after reading in your book about the effects on the human stock of a social organization based on economic reward I think we have a right to a good deal of gloom and alarm! The really depressing thing about a situation such as you describe is that, the evil being of slow maturation and coming to no obvious crisis, there will never be anything in the nature of a panic. And as recent events only too clearly show, it is only in moments of panic that anything gets done. Foresight is one thing: but acting on foresight and getting large bodies of men and women to accept such action when they are in cold blood—these are very different matters.

Fisher to Aldous Huxley: 3 October 1931

Thanks for your letter and for your sympathetic reference to the 'gloom and alarm' which, like the Djinn released from the bottle, seem to be the chief reward of my inquisitiveness. The demon is an old friend of mine now, and we are on much better terms than we were fifteen years ago, when he made so many things seem not worth doing, that I might well have thought there was nothing left. But the fact is that the more surely one realizes that the reasons for horror and dismay are not illusory, the more widespread and the more deep-seated they seem to be, the more unmitigated and exempt from natural compensation their destructive effects upon human nature, why, so much the more surely has one the rarest thing is this aimless and disillusioned world, something wholly and lastingly worth doing; and of how many of the little strumpet 'causes' that we dress up to discharge our loyalties upon, can anything like as much as that be said? I mean if we consider them as achieved and try candidly to evaluate the achievement.

I am fairly convinced that this need for something worth one's loyalty is pretty widely felt, (or sub-felt, for I suppose the subconsciousness has sub-feelings) among people naturally critical. The really impressive thing about 1914 was the eagerness with which men jumped to the conclusion that they had found something worth doing whole-heartedly. If there, sanity requires that it should be jealously guarded. And, though panic is certainly the way to move politicians, I am wondering if the mental requirements which drew educated pagans into schools of philosophy are not already operative in our own generation; and the Stoics, had they had a social policy, were certainly powerful enough to have won their way. But they were too defensive of the individual soul.

I appreciate immensely what you write on the laicization of our festivals. I do not in the least believe that merely scientific criticism of religious fables in history or cosmology is responsible for the loss of zest. The decay of interest, both in the religion, and in its festivals, must come from a failure to be moved to admiration or enthusiasm by certain ideals of human excellence. What is dreadful to think of is not the admiration of one type giving way to that of another—which, as loyal conservatives we may well dislike—but the decay of the entire power of recognizing human excellence of any sort; and certainly the later ages in Rome show as great a genius for factious mutual hatred and distrust as the Homeric poems or Chaucer show for admiring wonder.

That looks like one of the ugliest of my pot-full of bogeys.

To return to politics. Is it not a sheer gift that family allowances should happen, as far as one can judge, to be good economics? It is sheer luck, as inconsequent as a miracle; but it does suggest one alternative method to the stampede; that is to get important things done for unimportant reasons. I mean that much less real hardship would have been felt by the teachers and sailors by reason of the cuts, had the pay been simultaneously redistributed, giving each child say 10 per cent of the childless man's pay; and the conditions in French industry in respect of employment, and absence of strikes, since their system was adopted, might well make our industrialists' mouths water. What a horrid thought!

But it does look like a gift.

J.S. Huxley to Fisher: 4 May 1930

I have just finished your new book—all my spare time since Wednesday when I got home has been taken up with it—and must write and congratulate you on it. It does seem to me the most important book on Evolution which has come out this century.

I shall have to have a go at some bits of it again—mathematics is not my strong point, and quite apart from that I found some passages very obscure, if you will allow me to say so!—especially in the chapter on metrical properties.

I wish I had known you were doing this book—I would have liked to have talked over the Sexual Selection business—I have definite ideas as to the value in monogamous territory birds. Also I could give you a beautiful case of isolation creating a gene-gradient, p. 127 [*GTNS*, p. 141], viz. Sumner's Florida Deermouse. ... [*GTNS*, p. 151], E. Selous actually got observational evidence of marked differential success of male Ruffs in getting mates[59]. ... I can't see how you can omit all discussions of Haldane's papers—doesn't it come in to your scheme? You also don't mention Elton's ideas—I'd like to hear you on these. In reference to change of selection in man, I think it was Huntingdon who pointed out the enormous effect it would have to settle down to agriculture from nomadism and hunting—prudence and routine qualities would be encouraged—rashness and quest for excitement would very likely run off and join hunters elsewhere etc.—or go into the army and get killed. (This is in E. Huntingdon, *Human Habitat,* Chapman and Hall, 1927—quite worth reading).

There is also the selective effect of migration—e.g. Pilgrim Fathers weren't a random example of Britons, nor the first Australian colonists. Effect of migration on Ireland, on move to towns on country folks temperament. There are misprints ...

Again congratulations on the book.

Fisher to J.S. Huxley: 6 May 1930

I am extremely glad that you think well of my book, and want to thank you especially for writing so quickly and kindly about it. The importance which you and Haldane attach to it—and there are no two opinions in this country to which I would attach more weight—gives me much pleasure, but not a little embarrassment, for if I had had so large an aim as to write an important book on Evolution, I should have had to attempt an account of very much work about which I am not really qualified to give a useful opinion. As it is there is surprisingly little in the whole book that would not stand if the world had been created in 4004 B.C., and my primary job is to try to give an account of what Natural Selection *must* be doing, even if it had never done anything of much account until now. It struck me there was a great deal untouched in this line of country besides much confusion due to past neglect to be cleared up.

As you have seen I have often been tempted beyond these austere limitations and, judging from your letter, I shall be still more tempted in future. I should love to talk over sexual selection in relation to monogamous territory birds, some time when we can get together. Will you be saying anything about it in your broadcast lectures? You must tell me when we meet if you are with me as to the origin of sexual preference, and as to the very sweeping argument of the first chapter. ...

One thing I much regret is not mentioning Haldane's work in the preface as an example of the mathematical groundwork in biological problems which seems to me so much needed. Perhaps I should have mentioned Bernstein in the same place.

Many thanks for your other points ...

Fisher to J.S. Huxley: 24 September 1931

It has occurred to me that in our present paroxysm of crises the discussion in Section D may drift into economic topics;[60] and, in that case, you might find it worth while to have looked through the enclosed reprint [*CP* 82]. I am really rather proud of it, because it was written early in 1928 during the rising tide of fictitious prosperity and I tried to rub in that the non-rural industries would suffer in their turn, through the failing purchasing power of the agriculturists, which is just what has happened in the last two years. We are in the same position with respect to the failing purchasing power of Australia and the Argentine as New York and Philadelphia are with respect to the failing purchasing power of the Western States. Even Malthus would have recognized that the over-production of primary foodstuffs is a sign not of over- but of under-population. It may be useful to recall this in case MacBride or someone chooses to attack Family Allowances on the ground that we, or the world, are over-populated.

As someone may state or imply that Family Allowances would be an *extra charge* on industry, it may be worth recalling that they were introduced as an economy by the industrialists in the French post-war reconstruction, and the financial position of French industry compared to our own at the moment does not encourage the view that in this matter they were being extravagant and we economical.

I don't know that the subject will come up at all; but I send this brief memo. as I know how much more satisfactory it is to be prepared, even for the most unreasonable lines of attack, and I should not easily forgive myself if, when you were taking my part, some hostile zoologist had reason to think he had an opportunity of scoring off you.

I have now just had your note of the 23rd where you raise the question of introducing Family Allowances into your address. ... *If* you have time I am sure that Family Allowances as a constructive social suggestion would add greatly to the public interest in the discussion and, I am afraid, also to the divergence of biological views. To develop the subject as far as this in the short time would need a greater power of conveying ideas clearly and briefly than I myself possess, but I believe you could do it.

At least, if you try, you have my very best wishes.

J.S. Huxley to Fisher: 28 September 1931

Thanks for your letter and enclosures. I brought in something about family allowances, and I think it went off quite well. The discussion as a whole certainly attracted a very large audience, and a good deal of notice in the papers. MacBride made a long and rambling speech in which he made a bitter attack on you 'butting in', as not being a biologist! and therefore having no business to discuss these matters! ...

Fisher to J.S. Huxley: 29 September 1931

It was exceedingly kind of you to speak for me at the Population Discussion and I am glad you brought in something about Family Allowances. I was much disappointed in the newspaper accounts of the meeting, ...

I have had, however, an amusing account from Ford which he had from Baker telling me of MacBride's attack and of Baker's interruption. Ford writes with great indignation against MacBride but I half suspect he is doing me more good than harm. ...

Fisher to J.S. Huxley: 2 November 1931

I mentioned some time back that I had put together some stuff about objections to selection theory. It is at present quite incomplete and glancing at it some other examples might occur to you of the kind of thing I am combatting.

I have thrown the thing into the form it would take if I used it to replace the present preface to my book, which preface has entirely failed in the purpose for which I wrote it; for it was specially written in the hope that no reviewer could possibly review the book on it, and the majority have done so nevertheless—three sexes seem to be irresistible to them! So when a German edition was proposed I thought I'd have a shot at discussing some of the difficulties. The extraordinary thing, interesting too and half discouraging, is that in the history of each difficulty one can usually find a perfectly rational statement of it right at the beginning, while its later appearances become less and less rational, until it is twisted into some form which is logically almost unrecognizable. However, you will see what I am driving at if you look through the paper. Darwin has seen part of it and wants me to publish the stuff in some journal or review, whether I pitch it into my book ultimately or not.[61] Do you know any Editor that would care for it? ...

Fisher to J.S. Huxley: 23 November 1931

I am enclosing the paper on Dominance and a couple of others ... You will see that the dominance paper deals fairly thoroughly with the many sources of genetical evidence, but does not enter upon the broader subject of dominance as confirmation of the view that evolution has generally taken place in opposition to the direction of mutational changes, thus explaining the separation of the sexes, methods of ensuring cross-fertilization, etc., as means of avoiding undesirable recessives. This would need much more extended treatment, but is clearly the part of the story of wider interest. For the present, however, it seems best to concentrate on proving the case that dominance is an evolved phenomenon.

Fisher to J.S. Huxley: 27 November 1934

I am returning the three papers on Race, which you sent me. I cannot see anything particularly wrong about them. I suppose they should have a soothing influence.

I am glad you mention community of ancestry, which I think is an essential measure of racial similarity and, indeed, of genetic similarlity when applied to groups, rather than to individuals. However, there is room for difference of opinion even there.

I cannot think that in view of their racial tradition, our Hebrew brethren will find any permanent intellectual response in the conclusion that the word 'race' has lost any sharpness of meaning, or that it is hardly definable in scientific terms, ideas which seem attractive, only, I fancy, in the framework of current controversy.

J.S. Huxley to Fisher: 11 December 1940

To my surprise, I am finding great difficulty in getting any information, however rough, on the following point: what proportion of the adults of reproductive age in one generation produce what proportion of the children of the next generation?

I want this in some striking form for a popular article, and should imagine that about one-third produces about two-thirds. I would not mind putting down a guess and saying so, as long as I had assurance that it was not too far out. I can get lots of information as to the proportion of dependent children under 15 who come from, say, families with three or more children, but this is not at all the same thing. ...

It seems to me very curious that this has not been worked out, even approximately, as it obviously has very important selective consequences. There can be no other animal species with such a remarkable degree of differential reproduction among adults which have already reached reproductive age—and especially among adults who are actually reproducing.

You will be interested to hear that I have at last finished my Evolution book and am sending the final slip proofs in to the printers to-morrow—thank goodness!

Fisher to J.S. Huxley: 13 December 1940

I have hunted up one reference, I think the best, to the point you mention: D. Heron (1914). 'Note on Reproductive Selection', *Biometrika* X, p. 419, finds that 'approximately three-fifths of the males born die unmarried, and one-half of one generation comes from one-quarter of the married population, or from one-ninth of all the males born in the preceding generation'. Also, 'nearly half of the females die unmarried, and that half of one generation comes from one-quarter of the married, and from one-seventh of all females born in the preceding generation'. There is quite a useful diagram referring to the males on p. 420. These results are based on Australian data, death registrations 1912.

Naturally our own death registrations are useless, for they do not even require a statement of marital condition or number of children, if any, and this in spite of the relevance of these facts to the granting of probate. However, we can be quite sure that the facts are nearly the same in all civilized peoples.

I agree with you entirely that mankind must be unique in this enormous difference of reproduction among the adult and sexually mature—unless one counts in the adult but sexually imperfect social insects. Its chief importance to me lies in the fact that it supplies a medium in man for higher selective intensities than probably exist in any wild species, or at least to any long stabilized in their environment, whereas it has been constantly assumed and asserted that the reduction of the death-rates has abolished natural selection in man. I allude to Heron's conclusions and similar evidence on p. 190 of *Genetical Theory* [*GTNS*, p. 209].

It is sometimes assumed that the general fall in birth-rate must tend in the direction of equalizing reproduction, but I doubt if it has had any effect in this direction, and it might have the reverse effect.

Good luck to the book.

J.S. Huxley to Fisher: 16 December 1940

Thank you very much for your letter with the reference, which exactly fills the bill.

I entirely agree with what you say about the selective implications for man, but I had not thought out the conclusions to be drawn as regards the fall in the birth-rate, which are very interesting.

Fisher to J.S. Huxley: 5 July 1954

... About the polymorphisms,[62] I should myself stress the effect two gene substitutions may have on each other's selective intensity as the operative cause of close linkage, and it seems natural that such mutual influence is common with genes affecting the same characters, e.g. conspicuous pattern genes in the grouse locusts or *Lebistes*, and rather widely between loci influencing the same quantitative character, if such a character, as must be usual, has an optimal value.

What I felt rather puzzled about in 1930 was how, in spite of such widespread tendency to closer linkage, free recombination had in fact been retained, as is needed if different improvements are to be combined, though I find it difficult to understand how this *effect* is itself effective in promoting recombination.

Fisher to D. Caradog Jones: 12 December 1932

Many thanks for your kind letter. It is a pleasure to hear that what one has written has been enjoyed. I was, I think, very fortunate in my reviewers, but in spite of that it will evidently take a long while to make any impression on biological, or equally on sociological, thought. I should be very glad to hear, now or later, of your impression of the chapters on human selection. While writing them I felt they were growing unduly, as I had originally intended social selection in human fertility, following sexual selection, and mimicry, as a third development or application of natural selection, having, like them, special relevance to special circumstances. Whereas, in the other cases, I could take a groundwork from earlier writers, and could concentrate on critical discussion and amendment, in the human case I felt I had to justify the primary propositions, such as the heritability of fertility, whether consciously or unconsciously conditioned, and this took so much space, that I fear Chapters VIII to XII are not easily grasped as a single argument.

Again thanks for your encouraging letter.

Fisher to O. Kempthorne: 31 January 1955

I have been puzzling over your letter and paper[63] for some time, and maybe I have not got it clear yet.

I do not at all agree with the last sentence of the opening paragraph of your introduction, 'Later in 1941 Fisher showed that this is true only if the quantity Q^2/PR remains constant...'

What I said on the second page of the paper cited [*CP* 185] was, 'The direct mathematical measure of the average effect of a proposed gene substitution is the partial regression, in the population as actually constituted, of the genotypic measurement on the numbers 0, 1 or 2 of the allelomorphic genes in each genotype.' i.e. in that paper I set aside the experimental test of merely introducing more genes of any one kind in an experimental population, and measuring the change in average population value; I do this through recognizing that any gene substitutions do not merely act by substituting new for old genotypes, but that they ought properly to be regarded as also affecting the environment in which a natural population lives. Interactions with the environment are not, however, specified quantitatively in terms of the genotypic constitution of a population, but would require a full specification of the climatic and ecological situations in which a species finds itself.

For example, dominance deviation favouring, over a large number of loci, heterozygotes on the average over homozygotes, would in hermaphrodite plants favour the spread of genes having a variety of effects on flower size, colour, nectar secretion, scent, etc., and also other genes favouring self-sterility, if genes of either of these two kinds existed and were available for selection. If they are available, any improvement in the species, through increase of heterozygotes, may properly be ascribed to these secondary gene substitutions, leaving nothing over to be ascribed to the dominance deviations behind them, for these latter, by themselves, could produce no effect whatsoever on the evolution of the species; but a change in the attractions offered to insect pollinators, or an improvement in a self-sterility mechanism, would constitute such an evolutionary change.

My point here is that there is no quantitative relationship between the dominance deviation of the numerous effects first mentioned and the rate of evolutionary advance; but there is a quantitative relationship recognizable as specified in what I call the 'fundamental theorem', between the genetic variance[64] in fitness to survive due to the genes capable of influencing the frequency of cross-pollination.

Equally it should be noticed that external features of the specific environment, such as an increase in the numbers of particular species of insects, or a meteorological change favourable to wind pollination, is capable of raising the specific average through increasing the proportion of heterozygotes without any evolution being ascribable to the plant species.

Due to all this I am completely puzzled by the statement in your letter that the rate of evolutionary change may be equated to the total variance rather than to the genetic component of variance as I had done. I imagine that by 'total variance' you mean to include the dominance component and the total of epistatic components, but perhaps not the environment components in the actual variance. For my own part I think these are all in the same boat, even the last, for an environmentally induced variance in fitness, i.e. in capacity to leave a remote posterity, may, like the others, induce selection in favour of genes capable of enabling the organism to secure for itself an environment of the desirable type, and this, it seems to me, is exactly what happens as a consequence of the other non-genetic but genotypic component of variance. ...

Fisher to O. Kempthorne: 18 February 1955

I should be entirely satisfied if you cared to use the two quotations from page 56 of the 1941 paper, which seemed to express just what I mean. On your second page you say, 'I can accept the statements in your letter about secondary gene substitutions in that if the dominance deviations favour heterozygotes and hence favour secondary gene substitutions, then the resultant effects should be attributed to the secondary gene substitutions and not to the dominance deviation.'

My point is that the evolutionary improvement is due to the secondary gene substitution, and the evolutionary effects are constituted by such substitutions. It is not at all that the dominance deviations are ascribable to the secondary gene substitutions, as suggested in your following sentence.

... the only evolutionary effect, either in increased fitness or in anything else, that I can recognize as such, is constituted by the changes in gene ratio, and if by the extinction of certain insects a plant were rapidly to become generally self-fertilized and homozygous through lack of means to cross-pollination, I should, so long as the gene ratios remained unchanged, consider that the plant had not evolved but was reacting passively to its changed environment.

Sorry to be so long-winded about all this.

Fisher to M. Kimura:[65] *3 May 1956*

In considering the original statement of what I ventured to call 'the fundamental theorem of natural selection', I had, of course, considered the relation between such a situation and that in which a potential function existed, for my mathematical education lay in the field of mathematical physics. As you realize, I preferred to develop the theory without this assumption, which of course in another aspect is a restriction. Of course, I do not question that the selective intensities acting instantaneously may well be equivalent to those derivable from such a function, but I think it should be emphasized that both changes in time, that is in the environmental *milieu* and in the gene ratios themselves, that is the heritable constitution of the organism, will change this virtual function in a way that cannot be specified in terms of the quantities used in formulating the fundamental theorem.

Of course I realize that Sewall Wright has often argued as though such a potential function must exist, or as though all systems of forces were conservative, and in such systems, the idea of the mean fitness of the population has, I presume, a meaning more absolute or permanent than the mean value of the Malthusian parameter actually in being.

In answer to my question about in what respect you thought the fundamental theorem needed extension, you say that your original purpose was 'to obtain the general expression for the rate of change of population fitness'. Now, of course I purported to give such a general expression, and I should like to know whether your expression differs from mine in substance rather than only in form, and in what respect you think that my expression is erroneous. Of course I had developed the multiple allele case actually before the book was published, and have put it into the Dover Publications edition, which I hope will soon appear. I should like to be clear, however, that the expression I have obtained for the rate of change of population fitness by equating it to the variance in fitness at any instant, does not depend on the existence of any potential function. ...

Fisher to M. Kimura: 14 July 1956

... The possible interactions among different organisms can be specified either in respect of relationship, e.g. the mother yields milk well and her bull calf grows to be big, or specifiable by interaction between different genotypes in the same locality, such as you are considering, or the effects of genotypic differences on the mating system, such as I considered in the paper you refer to [*CP* 185], but I can only think of them in general as parts of the environment in which the advantage, or disadvantage, of any particular gene is determined.

For example, it has probably been widely true among hermaphrodite plants that products of self-fertilization do not themselves bear so many seeds, or have so many offspring, as the plants from the same mothers by cross-fertilization. Whatever this may be due to, and of course I think a rational theory has been put forward, it will certainly have as one of its effects that the heterozygotes of any gene pair are, on the average, at an advantage compared with the two corresponding homozygotes, from a cause quite independent of the developmental sequences induced by these genotypes. This would add a component to the genotypic variance of fitness, which, in the hypothetical case of gene ratio equilibrium, would be without effect on the gene ratio concerned, and therefore on evolution, due to change in this gene ratio.

It has, none the less, manifestly had very important evolutionary effects, and these are due, and in my formula are ascribed to, variants in other factors such as might affect the size of petal, the brilliance of pigmentation, the abundance of nectar, the scent of the flower, or any other characteristic aiding, or encouraging, the process of cross-fertilization. In fact, the non-genetic genotypic component concerned would be without evolutionary effect save for the existence of variants in these other factors. In the meticulous accountancy of biometrical genetics it must be ascribed to these factors, but I cannot think it misleading to say that the widespread advantage of the heterozygote has as its evolutionary effect the development of apparatus, or of a mating system, favouring cross-fertilization, or in animals the development of separate sexes. ...

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