Fisher to R.S. Koshal: 7 July 1938

I will answer first the genetical part of your letter. If s parent lines had been used with the complete set of $\frac{1}{2}s(s-1)$ first cross progenies, one could pick out $s-1$ comparisons among the $\frac{1}{2}s(s+1)$ sets of samples available, using the form

$$\begin{array}{l} 2\,\mathbf{AA} + \mathbf{AB} + \mathbf{AC} + \ldots\ldots\ldots\ldots\mathbf{AZ} \\ 2\,\mathbf{BB} + \mathbf{AB} + \mathbf{BC} + \ldots\ldots\ldots\ldots\mathbf{BZ} \end{array}$$

s items

These would compare the effects of the whole sets of genes **A**, **B**, etc, characteristic of the s parent strains. The comparison enables one to say which varieties give generally the best results on crossing.

In addition the material gives $\frac{1}{2}s(s-1)$ comparisons of the form

$$\mathbf{AA} + \mathbf{BB} - 2\mathbf{AB}$$

i.e. the double value of each cross may be compared with the sum of the performance of the two parent lines. The effect known as heterosis is that in some species and in some characters these comparisons would be predominantly negative; consequently their total contributes a single comparison for heterosis, or, as it may be called, for dominance bias.

There remain the $\frac{1}{2}(s-2)\,(s+1)$ comparisons representing the variation among the last lot of $\frac{1}{2}s(s-1)$. In Calcutta I think I spoke of these as due to epistacy, but this is a wide use of the word, and it is difficult to name the effect, if it exists, in genetic terms. Since in each comparison direct additive effects of the genes are eliminated, it clearly can only depend on the way different genes interact, and this is generally spoken of as epistacy.

I liked your analysis of the three cotton lines, showing in that case that the genetic comparison alone explained the observations, neither heterosis nor epistacy having any appreciable effect. I think this may often turn out to be the case, but the plant breeder will find it useful when departures from such a simple rule are indicated. ...

Fisher to A.G. Lowndes: 23 June 1945

Thanks for your offprints and letter. My point[66] was to stress what is sometimes overlooked, that natural selection will only explain adaptations insofar as they are effective in preserving the germ plasm of the individuals concerned. This does not preclude adaptations which are effectual through the survival of relatives, for these share to a greater or less extent the germ plasm of the individual. So the parental instincts, though altruistic, are accessible to improvement through natural selection, and in my book I do discuss how far we may think of the development of nauseous flavours in insect larvae, at least where these larvae are gregarious and not [living?] singly, without postulating that a larva, once tasted, can survive, which was

the point upon which Poulton always relied. I wanted to avoid the assumption that an instinct, such as the avoidance of cannibalism, which might be conceived to be beneficial to the species, could have arisen unless it also furthered the survival of the individuals manifesting it. I think this distinction is needed to avoid the multiplicity of meanings of such phrases as 'beneficial to the species'. Of course, the instincts of carnivorous animals which care for their young must be very sharply inhibited to prevent them regarding these as prey, but natural selection would not explain any gentlemen's agreement among dogs not to eat each other.

There are a number of instances of tendencies which have been developed apparently clean contrary to the general interest of the species, while they have favoured individual survival. I think a good example of this is in the sex-ratio of polygamous animals living naturally in flocks and herds, where the economy of the herd as a whole would seem to suggest (and the stock breeder would prefer) a sex-ratio of about 5% males, but where Nature, through the action of a type of selection which I discuss in the chapter on Sex, insists on producing nearly equal numbers of the two sexes. Another and more widespread example is in the evolution of dominance to deleterious mutations, for the effect of this is merely to allow the deleterious recessive to increase in numbers, so affecting the inheritance of more individuals, while keeping the number of defectives eliminated at the unchanged level required to balance the mutation rate. Mechanisms of cross-fertilization act, at least for short-range purposes, in the same way of avoiding the immediate injury of exposing deleterious recessives to selection at the expense of allowing them to accumulate, until in many plants and animals even slight inbreeding is quite dangerous. ...

Fisher to S.A. McDowall: 19 November 1931

I am very glad you liked my old dominance paper—I think it was the 1928 one [*CP* 68] you referred to. It was quite a revelation to me when I first realized that the failure mutations, which cannot effect direct evolutionary changes, have yet left their marks so extensively on the species in which they occur. One might, in fact, make a chain of effects, (i) deleterious mutations become recessive, (ii) the recessiveness of defects makes homozygosis dangerous and gives an advantage to cross-fertilization over self-fertilization, (iii) separate sexes in motile animals and some plants, separate inflorescences in others, and devices to ensure cross-fertilization. A further development in this line has recently been found among the midges, families of small diptera, where many genera are now known to have unisexual broods, produced by male-producing females and female-producing females, which are genetically different in the sex-chromosome. Thus brother by sister matings, which would otherwise perhaps be habitual,

through the short lived flies hatching out at the same time, are precluded in these species. The selection in favour of all these arrangements seems to arise entirely from the individual advantage of avoiding the exposure of the underlying recessives, for the racial advantage would rather lie in the other direction, in bringing them to light and eliminating them. ...

Fisher to A.H. Machino:[67] *9 December 1948*

The point of my contribution to the discussion of the Lysenko speech was that certain inferences could be made from the words used by Lysenko himself, and that to this extent the issue could not honestly be evaded, as it would appear Haldane would like to do, on the grounds that certain contributions made in Russia might not yet have been fully studied in Western countries, and that certain 'scientific' claims have not been exhaustively disproved.

The inference I make from Lysenko's speech, and this inference is justified solely by the excerpts chosen, is first that he is not a scientist, however cranky, in that his object is not to establish the truth, and secondly, that he is not interested in the welfare of Russian peasants, although we can imagine such a benevolent interest to be in fact very ignorant.

He is, as his address shows, an advocate and partisan, concerned to grasp power by successfully 'winning a case' before the court of appeal, represented, I suppose, by one of the political bureaux of the Party.

I do not think I can write all this over again in shorter space than that taken by my British broadcast. I imagine you are entitled to quote the latter for broadcasting to Russia, but I do not think you can leave out the quotations without missing the only point I have to make.

Fisher to J. Marchant: 24 November 1938

Perhaps the discrepancy between National Statistics, showing little or no fall in birth-rate for the last few years, and the experience of doctors lies in a change of attitude, rather than a change of practice.[68] I mean that many ignorant people who, in the past, practised various methods of birth control surreptitiously, now realize that it is proper to ask medical advice.

So far as I can judge, it is a complete, but very widespread fallacy to think of these practices as having spread from the socially upper to the socially lower classes during the last two generations. There is no sign of this, at least, in our rather inadequate data on birth-rates of different classes at different times, and I remember Dr. Brownlee producing extensive data to show that different districts, containing very different proportions of well informed and ignorant people, in fact changed their birth-rate nearly simultaneously. One must remember that the early propaganda by pioneers like John Stuart Mill was particularly directed at the poorest classes, and

that the hardships entailed among them by large families have been constantly insisted on by neo-Malthusian advocates. I should say, and Heron's figures support this, that there was a clear differential fertility at least as early as 1851, and that this has increased rather than diminished ever since, but that the main feature has been a simultaneous diminution of birth-rate in all classes, approximately in proportion.

Much publicity has been given to some data from Stockholm[69] purporting to show a higher fertility among the better paid, but in Sweden as a whole it is certain that the poor have the larger families, and it is probable that the data from Stockholm are greatly affected, as in the case of other large cities, by a segregation within and without the city area between wage-earners with children living largely outside, while wage-earners without children live in blocks of city flats.

If you take family allowances in their fullest sense as meaning allowances sufficient in magnitude to give an equal standard of living to parents and non-parents doing equivalent work, then the family allowances offer no bribe for parenthood; they merely annul the existing economic bonus for refraining from parenthood. They would leave the question of procreation to be settled exclusively by considerations other than the immediate economic necessities of the family, e.g. either the health of the mother, the environment of the home, the parents' beliefs in respect of the national interest, of over- and under-population, on the opinion of neighbours, etc. The only change would be that the prudential considerations on the future economic prospects of the offspring would no longer be a motive for family limitation.

These considerations, other than that of economic pressure, seem, on the whole, to be eugenic in their action, especially with respect to health, and a confident optimism with respect to the world's future. In fact, if an effective system of family allowances were in action, I should not think of dissuading parents from limiting their families to zero if they thought that was in their own, or in the public, interest.

Fisher to K. Mather: 18 May 1934

Thank you for your long and interesting letter ...

About Sewall Wright, he has changed his ground so frequently since I first published on Dominance in 1928 that I am not quite sure what his alternative theory is supposed to be. After all, I suppose that a theory must always be an attempt to deduce some admitted phenomenon, which is regarded as requiring explanation, from causes the working of which is supposed to be understood. Wright makes a good many general assertions, many of them quite acceptable, but I cannot disentangle any coherent

theory from them. This may be because I am still occasionally trying to work in points of views which he has now abandoned.

It is quite obvious that in a chemical reaction one ingredient may be present in excess, in the sense that small variations in its amount have very little effect on the speed of the reaction, while a large diminution of it would slow the reaction down. That this is probably the case with the products of some genes is shown by Stern's 'bobbed' allelomorphs. It is a relatively obvious way of producing dominance against mutations which partially inactivate the mutant genes. It might, as far as my theory is concerned, be the only mechanism by which dominance is produced, though I do not imagine that this is so. But if this were so, the occurrence of dominance would be just as much in need of explanation as if dominance were produced by some other mechanism. For the fact that one component of a reaction is present in excess implies that its speed is regulated by other components, and that mutations affecting these, if they occurred, would not be recessive, whether the mutation reduced the activity or enhanced it. On the theory of components in excess we should have to say that the organism had been so modified that the speeds of all biochemical processes were regulated only by the products of genes incapable of mutation.

Actually, I think ... much of Wright's argument turns on the very well authenticated fact that the wild type is much less variable than are the mutant types. This seems a good fact of observation which can be understood if modifiers have been worked into a system of checks and counterchecks to stabilize the normal course of development, but which naturally fail when development is in any important degree abnormal.[70] I am not at all unwilling to regard dominance as a particular case of this more general phenomenon, but I am quite unwilling to say that we understand this general fact except as due to an evolutionary process by the selection of modifiers, or that it is available on its own merits as an explanation of the particular case offered by dominance. ...

Fisher to K. Mather: 7 January 1942

... As to the *sheltering* question [*CP* 133], I imagine the disadvantage which accrues to a potential, but not incarnate, homozygote must be due to interaction of other factors with that for heterostyly itself. I do not think there is any ground for expecting in the neighbouring of the S locus an accumulation of genes having unconditionally any deleterious effect; but throughout the whole germ plasm there may well have accrued genes which react less favourably with **SS** than with the other two phases of the heterostyly factor. ...

Fisher to K. Mather: 5 February 1942

I am very glad you have taken up the discussion started by Espinasse[71], for

you are one of the few people capable of doing it properly and setting the present position of genetics against its proper background. ...

As a tradition, though of course not as a science, genetics is exposed more indefensibly than you seem to admit to the criticism of being anti-Darwinian, not in the Russian sense of theological heresy, but in the equally damning sense of factiously attacking and trying to discredit the far-reaching and penetrating ideas on the *means* of organic evolution which Darwin had originated. It was not only Bateson and de Vries, but almost the whole sect of geneticists in the first quarter of this century, who discredited themselves in this way. The ideas of this period are permanently embalmed in amber in Morgan's mind. Writer after writer asserted, or implied, as though it were a demonstrable fact, that species arose by single mutations, and that selection of small continuous variations within the species was known to be inoperative pending the arrival of an appropriate mutation. Continuous or normal distributions were identified by de Vries with non-heritable fluctuation. The idea of polygenic Mendelism was frowned upon by both the biometricians and the geneticists when I published the paper you cite [*CP* 9] in 1918. It would not have been published had not the cost of publication been reimbursed to the Royal Society of Edinburgh by my friends.

I am very glad that Dubinin has grasped, as you mention, the fact that particulate inheritance, so far from being antagonistic to Darwin's main theory, actually removed the principal difficulty with which it was encumbered. This assertion was entirely new when I put it forward in 1930. Indeed, before that time I doubt if anyone had taken the trouble to understand why Darwin should have concerned himself so much with Lamarcoid effects of changed conditions and increased food as the causes of variation, although, as he shows in many passages, he was clear that, as regards *evolutionary* effect, such factors were quite subsidiary. The whole distinction between mutation and evolution latent in Darwin's thought was ignored by de Vries and Bateson, and entirely obscured throughout the infancy of genetics. ...

Fisher to K. Mather: 10 February 1942

Thanks for your letter. If you learn anything further of Timiryazev, I should, of course, be glad to hear it, though, as you say, there is nothing to build high hopes on. It is only too common, both in England and abroad, for biological writers, even those capable of meticulous care and self-criticism in matters of factual detail, to be entirely without these restraints in abstract or theoretical statements.

Levit, however, who had, I think, a central laboratory in Moscow on human genetics, was lecturing on the *Genetical Theory* very soon after its publication, and had a panel, I suppose of his students, at work on its translation into Russian. I remember being offered 1000 Roubles, apparently in

compensation for the infringement of copyright.[72] I remember it because they were only available at the expense of visiting Russia where they could be expended. Anyway, my book was well known in Russia quite early.

Fisher to K. Mather: 16 February 1942

I have been reading Lewis's very useful paper on the evolution of sex in flowering plants, in *Biological Reviews*.[73] There is part of it that makes me wonder whether I really got my argument across in the section 'Natural selection and the sex ratio', pp. 141-143 in the *Genetical Theory* [*GTNS*, pp. 158-60].

If natural selection were determined by 'the advantage of the species', whatever definition might be given to this, I suppose that, as a stock breeder finds he can do very well with one bull to 20 cows, Natural Selection ought to have been expected to produce such a ratio in large herding ungulates; but it hasn't, and I think the section referred to does supply the reason. The same should, I think, be true of dioecious plants; if there were but one male to 20 females, and even if this ratio were sufficient to ensure adequate pollination of all ripe stigmas, then, on the average, every male plant contributes 20 times as much to future generations as a female plant, and the individual parent would gain great selective advantage if its style mechanism were such as to produce a high proportion of males. Setting aside small factors, such as differential viability of the sexes, this would lead to a stable sex ratio near to 50%, by reason of individuals competing to contribute to future generations, though this might be not at all necessarily advantageous from the point of view of the species as a going concern.

I make this point because, if it is right, species such as the two *Humulus* and two *Rumex* in Lewis's table do present a special evolutionary problem, and are not to be accounted for by saying that one male is quite enough to fertilize a large number of females.

If this argument *were* sufficient, the animal kingdom with its commonly separated sexes would present a very different picture.

Fisher to K. Mather: 21 February 1942

Thanks for your letter. ...

I am glad of what you say about Lewis, that he is writing to me, and to hear also what you say yourself of some of these transitory situations being, perhaps for that reason, imperfectly adjusted. This seems to me a line of thought well worth exploring.

If you were to make a survey of the whole of some extensive genus e.g. Leguminosae, classifying each species as

a) Apogamous, or effectively asexual;
b) Hermaphrodite, and strictly self-fertilizing;
c) Hermaphrodite, and normally outcrossing;

d) Seldom or never self-fertilizing owing to protandry, a self-sterilizing factor, heterostyly, etc., and
e) Dioecious;

would you get evidence that the central condition of hermaphroditism was so wide-spread, i.e. present in every taxonomic branch of the assemblage, and so common as reasonably to be thought present in all phylogenetic stems, and that both extreme conditions occurred sporadically only in isolated species, or groups of species? I do not know that anyone has systematically assembled the evidence from any considerable family or natural order. It seems to me most important for purposes of interpretation that this should be done, for, theoretically, it might be that one of the extreme conditions was more universally present in the ancestry, though continually throwing off side-shoots towards the other extreme.

Fisher to K. Mather: 3 December 1942

Thanks for sending me your article for *Nature,*[74] with which, of course, I find myself very much in agreement.

With respect to my own work, it might be worth while referring to the paper of 1927, 'On some objections to mimicry theory: statistical and genetic' from the *Trans. Ent. Soc.* **75**: 269-278, [*CP* 59] where the notion of a gene acting as a switch was first developed ... .I should not like people to come to think that my interest in the modifiability of gene action was confined to, or dated from, the 1928 paper on Dominance [*CP* 68]. It would be truer to say that in 1928 it first occurred to me that *even* in respect of dominance the effect of a factor was conditioned by other factors.

Waddington does not use the phrase, but would it not be clearer if he had spoken of the canalization of the phenotype rather than of the genotype? I imagine that the important effect is always that in certain regions within the range of phenotypic expression, the phenotype is very much more sensitive to genic substitutions than it is in other phenotypically definable regions. These last regions we can speak of as buffered, or stable, while the first are unstable and appear as pathological compromises between two possible consistent policies.

It will be interesting to see how terminology develops to cope with this sort of idea. ...

Fisher to K. Mather: 23 February 1943

I am returning now this fat paper on Australians,[75] and see what you mean about pruning. Whatever may happen ultimately to the paper, I am sure it would be of service to the authors if you could give so much trouble to the matter.

Psychologically, I think—and this of course is nothing to do with the paper's fate—that they have got hold of the wrong end of the stick. I mean

that the human race seldom or never notices good results, least of all from innovations, nearly all of which are done with rather a guilty conscience, just as the first inventors of printing doubtless regarded themselves as swindlers for foisting off this cheap substitute as honest-to-God manuscript. On the other hand we *are* capable of noticing anything sufficiently alarming or grotesque in the way of bad results, especially if these can be connected with anything so guilt-provoking as sexual intercourse. Many African peoples regard the appearance of twins as an accusing finger pointed at their own duplicity. Deformities, imbeciles, and albinos must be alarming phenomena to primitive parents, so long as they are unfamiliar and inexplicable, and the long period of dependent childhood in Man gives the parents a chance to fret about their causation and to exaggerate the guilt of their early misconduct. I doubt if a completely albino tribe would recognize normal pigmentation as a 'good result' of anything whatever.

To me it is puzzling that mankind should have passed through what must have been a very long phase of inbred nomadic kindred-groups, with perhaps no more than six to ten fertile women in each, without eliminating completely the animal instincts for the avoidance of incest. However, there is no doubt that they are extremely strong and wide-spread in Man and that a good many rare and alarming recessives are common enough, at least to cause occasional alarm. ...

Fisher to T.H. Morgan: 11 October 1932

I have taken, as you see, some time to consider the big book,[76] of which you were good enough to present me with a copy. I thought, however, that you would prefer this rather than have me form a hurried and therefore an inadequate opinion. I think you will agree with me that one of the chief reasons why, in spite of raising so much dust, we are not making in this generation more rapid progress, is that we do not really give ourselves time to assimilate one another's ideas, so that all the difficult points, the things really worth thinking about, have to be thought out independently, with great variations in efficiency and success, some hundreds of times.

You will not want me to say, what is obviously true, that your book will for many years be a milestone in the progress of genetics, and in its application to evolutionary problems. I should rather say something which perhaps has not been said to you before, namely that in trying to assess the effect of the book as a whole I believe you have erred in underrating the effect of Morganismus upon the interpretation of genetic facts in relation to theories of evolution. Several particular passages suggest this to me, in which you take up discussions originating about the beginning of the century, without stressing to the unobservant reader that almost every term in our vocabulary has been given a sharper definition by the *Drosophila* work, so that a state-

ment which was merely plausibly vague in 1905 is highly precise and scientific in 1932.

This criticism, which I feel sure you will want me to state frankly, seems to me to be well illustrated by your use of the term Mutation Theory, as though the views we owe to *Drosophila*, and her devotees, were at all to be recognized in de Vries and Bateson. It seems to me that it is almost entirely through the work you initiated that we know something about the frequency and nature of mutations, and this knowledge may be regarded not only as completing the basis for a particulate theory of inheritance, but equally as destructive of the crude hypothesis of the early Mendelians, that mutations alone could 'explain' evolution.

I should bore you if I developed this further. Instead, if you really want to be bored, I enclose an offprint which has just come to hand of a lecture I gave last January to the Royal Society of Dublin [*CP* 98]. I do feel about your book, however, that you leave to us Drosophilophils abroad a lot of the explaining of how much we owe to that *genus*.

I hope you duly received $8 from me, through Dunn. Many thanks for the loan.

Fisher to C.S. Myers: 6 December 1932

... I want especially to take up the question you put to me, in your letter of 17 November, as to fertility, as this seems to be vital to the whole sociological aspect of what I was talking about.[77]

I do not want in the least to rule out voluntary infertility, whether it takes the form of celibacy, prudential postponement of marriage, or contraception. In each case the stringency with which it acts must depend, not only on the environing circumstances, but on the individual's reaction to them; indeed, this is part of what we mean by a thing being voluntary. If I want no more children, that is *my* reaction to my environment, just as definitely as though I had never wanted to get married, or as though I had never been conscious of the reaction as a personal choice, and the traits of temperament which influenced my choice must be as heritable as other traits of temperament. Indeed I imagine that by appropriate psychological tests applied, say, to undergraduates, you could pick out the traits which make for early marriage, and get a correlation with subsequent performance, in the same way as with vocational tests, or directly with size of family for that matter, though I suppose the women would be the best subjects for this. So the voluntary causes of the variations in fertility fall into line with the involuntary, and, being at the moment (for all I know, generally) much the more important, they add greatly to the force of the argument.

One may say that the richer classes practice birth control more stringently than the poorer because they are already flooded with types of temperament likely to set a high value on its advantages, and a low value on its disadvantages; whose parents and grandparents have been promoted into these classes partly for this reason. After all, it is not historically true, often as it is asserted, that birth control started in the upper classes and spread downwards. The early propaganda of the Neo-Malthusians in the '60's and '70's of the last century was deliberately aimed at the poorest strata of society, where the economic and moral case for limitation was strongest. What is true is that the practice spread quickly and far among the well-to-do, and slowly and not so far in the poorer groups.

You ask me what is 'proved'. I should say that undoubtedly Galton proved his case as far as the peeresses were concerned, and later peerage statistics show an appreciable positive correlation in the size of a peeress's family, not only with her mother, but with her *paternal* grandmother. There are also a good many other miscellaneous facts which do not square with the notion that the difference in fertility is due, even principally, to the difference of social tradition of different classes. For example, the people in the American *Who's Who* have been classified according to the extent of their education, and those with the best education have larger families than those with a poorer education. If it had been social tradition, one would have expected those with a poorer education to retain some of the characteristics of the class from which they originated, in fertility as in other things. Actually what we seem to have is merely the more rapid promotion of less fertile than of more fertile strains. Again, in mixed schools, such as public elementary schools, drawing pupils from a wide social range, there is usually a negative correlation between intelligence and size of family, whereas it appears from the Yale statistics that the children from families of 6 or more are the most capable, on a variety of tests, and the only children the least capable, that they get. Not, I imagine, because the most capable people have the most children, but because a lower measure of success will send an only child to Yale, than would be needed to send one of six or more. In fact, if you equalize the 'start in life', there should be a positive correlation between fertility and ability; and I do not think any other view makes sense of this. ...

... As far as the British statistics go, it seems that the class difference of reproduction is due to more celibacy, plus later marriage, plus more birth control; and I should be reluctant in any case to postulate three different agencies in the social environment all happening to pull in the same direction.

Fisher to R.K. Nabours:[78] *10 September 1929*

The remarkable genetic situation found by you in several polymorphic species in Tettigidae, will, it now seems likely, throw light upon a whole group of cases of polymorphism, combined with dominant variants, and little recombination of the factors. There is one group of facts of which

perhaps you are already in possession, or in a position to obtain, which will have an essential bearing upon the interpretation adopted, namely the frequency of occurrence in nature of the recessive, and of its several dominant variants, including combinations of these, if such occur in nature.

I imagine that counts of 1000 wild specimens from each of a number of suitable localities would be sufficient to determine the gene ratios with sufficient precision, and possibly you have records or preserved specimens on this scale. In any case I should be very much obliged if you could let me know the frequencies observed in such enumerations as are available, and if these are not sufficiently numerous, if you could possibly arrange that collections should be made on a sufficient scale to determine the frequencies. The most important species is *Apotettix eurycephalus* (Hancock) of which the genetic data are I believe much the most abundant.

It is of course essential that the counts should be based on material the collector of which takes all wild specimens which come his way, and is not specially concerned to secure the rarer varieties. I suppose therefore that collections deliberately made for frequency determinations will alone supply satisfactory data.

Fisher to R.K. Nabours: 21 October 1929

Many thanks for your letter. ...

I had scarcely expected that the frequency of Tettigidae types would have been already determined. Perhaps I may explain the connection in which they will be of especial interest.

The species you have investigated show a relatively common recessive type, and a number of rarer dominants, the dominants usually lacking dominance *inter se*, but showing usually complete dominance to their common recessive. At first sight this genetical situation, which may perhaps be paralleled in *Lebistes, Helix*, etc., seems the direct reverse of that found in multiple allelomorph series in Rodents, and *Drosophila*, where we regularly find a prevalent wild type dominant to a number of rare recessive mutants, showing no mutual dominance. I have argued from these cases that the prevalent wild type must in some way become dominant to its rare mutant competitors, else such a rule would not continue to be observed during an evolutionary progress in which numerous gene substitutions have taken place; and I have suggested the selection of modifiers affecting the appearance of the heterozygote as a possible means of this being very slowly brought about. The cases in Orthoptera and in other polymorphic species, showing an apparent reversal of the usual phenomenon, are therefore likely to throw new light on the question.

The most severe possible test of any theory is to draw all its possible consequences in conjunction with observed facts. If any necessary consequence is found to be certainly false, the theory goes. If new consequences,

not otherwise to be expected, are found to be true in fact, the theory is strengthened.

To test the theory of the modification of dominance by selection, one might argue thus. A number of colour patterns in *Apotettix* are clear dominants to the standard recessive; therefore these colour patterns are on the average somewhat more favourable to survival than that borne by the recessive. But they have not replaced the recessive in nature and must be regarded as in stable equilibrium with it in respect of numbers. Stable equilibrium is most simply assumed if the heterozygote has some advantage over both homozygous types. This agrees with the inference that the heterozygote pattern is more advantageous than the recessive, but requires in addition that the homozygote must suffer some disadvantage. Since there is no visible difference in pattern this disadvantage must be sought elsewhere, and is possibly constitutional. In testing this I find that in your matings between heterozygotes between two dominants, of generalized type $\mathbf{P/Q \times P/Q}$, there is in fact an excess of heterozygotes and a deficiency of homozygotes, on the average of about 7 per cent. This then is a new inference not otherwise expected, but found to be experimentally verified. A very special interest of such cases of balanced selection is that they afford a unique means of measuring a selective advantage in nature. For if the three types $+/+$, $+/\mathbf{P}$, $\mathbf{P/P}$ leave descendants in fact in the ratio $a{:}b{:}c$, then the gene ratio $+{:}\mathbf{P}$ will settle down to a stable equilibrium at the value $(b\text{-}c)/(b\text{-}a)$. If $b\text{-}c$ is due wholly to constitutional causes measurable at least approximately by survival in culture, then $b\text{-}a$ can be inferred from the frequencies in nature. The principle is one which I have often wished to apply, but have never yet come upon so favourable a case.

The full story of these polymorphic species must be exceedingly complex; they all seem to show excessively little recombination, and this I believe may be the reason why modifiers can modify the heterozygotes, but not, as would be thought more directly advantageous, modify the common recessives. This if true would depend on the rate of supply of advantageous mutations generally, and may prove later to be of greater evolutionary importance in supplying some sort of a gauge of the rate of evolutionary progress. However, this would be much too long a subject to go into in a letter which is already too long.

Fisher to R.K. Nabours: 30 December 1929

... I am very glad you raise the question of the viability of $+/+$. The *eurycephalus* data I worked through had too few matings involving this type to settle the question, but it is one which could be easily settled if, without neglecting the linkage work to which the bulk of your matings are devoted, a series of comparable extent were devoted to the question of viability. To test dominant forms individually to determine whether they are hetero-

zygous or homozygous would be laborious, and probably cut down the numbers so low as to be useless, but this can be avoided by making experiments in pairs.

(a) **P/Q** × **P/Q** giving **P/P**, **P/Q** and **Q/Q**.

(b) +/**P** × +/**Q** " +/+, +/**P**, +/**Q** and **P/Q**.

A sample of 5000 young from each type of mating would then give the viability of **P/P** and **Q/Q** in terms of that of **P/Q** with a standard error about 3½% and that of +/+, +/**P**, +/**Q** in terms of that of **P/Q** with a standard error about 4%. The comparison of heterozygotes with homozygous dominants may be derived with about 5.3% standard error. I dare not suggest much larger numbers, though these would increase the precision of the comparison, but it would be worth while to breed about one-third more of mating (b) than of mating (a).

As regards particular factors, in your published data for *Apotettix*, **Y**, **O**, and **RK** showed individually significant deficits of homozygotes, but **K** alone showed an apparent but not significant excess. It would therefore be especially valuable to include **K** in such a further experiment as I suggest. For the rest I suppose one should be guided by ease of discrimination. I should certainly use single genes rather than complexes in such tests.

I have, as you suggest, material for a paper on the subject, but I feel strongly that the conclusions to be drawn may be too important to be based on gleanings from your published data, rather than on *ad hoc* experiments, in which you can assure yourself that the ratios to be determined have been fairly arrived at. Also the full advantage of the viability determinations will only be reaped in conjunction with determinations of the wild frequencies. I should be most happy to collaborate either in a joint paper or by simultaneous publication, should you find it possible to devote some of the space and time available to these points.

Fisher to R.K. Nabours: 16 August 1930

Many thanks for the two reprints, which arrived with your letter today. I am very glad to hear of your plans for collecting.

As in all observational work it will be difficult to do enough to answer all the questions which present themselves. In this case especially the difficulty will be to reconcile the claims of large local collections (large enough to give a fair idea of the frequency of the rare types), and comparison of different localities, which can only be done if each local collection is fairly large, but which is certainly of too great interest to be ignored.

After some cogitation I should guess that collections of 1000 each from 10 localities would certainly be more informative than a single collection of 10 000, and would certainly be easier to deal with than 100 collections of only 100 each. It is of course conceivable that the last type of programme could be so skilfully planned as to be the best of all, only it would need a great deal of consideration, and more knowledge than will be available before your 1930 collection is made.

I am glad you were interesed by my book. It was unfortunately written too early to include the speculations on polymorphism, which seem at present to constitute a very pretty extension of Dominance theory. ...

Fisher to R.K. Nabours: 8 August 1932

I have received a very interesting letter from your assistant on the proposed collection of grouse locusts. Unfortunately, I have lost his letter and therewith his name, so I am replying through you. I should in any case be glad for you to see my letter.

[Enclosed letter]

I received your considerate letter on the proposed enumeration of the *Paratettix* phenotypes by collections from nature a fortnight ago, immediately before my departure on a short visit to Scotland. On my return I was much disappointed to find that your letter had been mislaid: and I am therefore replying to you via Dr. Nabours and without the advantage of having your letter before me.

I am exceedingly glad to hear of the research you have undertaken, as it appears that polymorphic species, at least those showing polymorphism of the same type as the grouse locusts, offer a unique approach to some of the most fundamental problems of evolutionary modification. You will perhaps have already seen the papers in the *American Naturalist* [*CP* 87] and in *Biological Reviews* [*CP* 93], in which I suggest an interpretation of the genetical situation found by Nabours in this group. For your convenience I enclose copies of both papers. The evolutionary history is likely to be in many ways more intricate than that which I have suggested and your researches may well open up unexpected developments. All that I have attempted is to sketch the broad features in outline.

There are in Nabours' published experiments strong indications that the homozygous dominant is somewhat less viable in the conditions of culture, and presumably also in nature, than the corresponding heterozygote. But this may, I think, be ignored in estimating the gene ratio. Thus, even if a particular dominant phenotype appears in as many as 36% of the sample taken, this leaves 64% as recessives, or 0.8 as the proportion of recessive genes, leaving 0.2 for the dominant genes and only 4% homozygous dominants on the assumption of equal viability and random mating. Even wih this high proportion, then, eight-ninths of the dominant phenotypes captured will be heterozygotes and it would make very little difference to one's estimate if the 4% of homozygotes had really been depleted by about a twelfth, owing to lowered viability. As far as this is concerned I believe

the gene ratio could be inferred with confidence from the frequency observed in the sample.

As to the accuracy with which it could be determined, if the sample consisted of 1000 insects a count of 640 recessives (in respect of any one factor) would be affected by a standard error of about 15. The proportion of recessive genes, and therefore also of dominant genes, would have a standard error about 0.01, and the gene ratio, 4:1 in this case, would have a standard error little more than 5% of its own value. This seems a very satisfactory level of precision. The point of determining the gene ratio lies in its being equal in a state of statistical equilibrium to the ratio of the selective disadvantage of the two homozygotes, compared in each case with the heterozygote. Thus, if in any particular case the dominant homozygote is at a selective disadvantage of 8%, owing to inferior viability, and this is the average value I find from Nabours' data on *Apotettix*, then a ratio of four recessive genes to one dominant gene would indicate that the recessive genotype in nature was at a net disadvantage of only 2%, and to determine so small a quantity with a standard error of only about 5% of its value would be beyond the precision even of laboratory experimentation and almost infinitely beyond our very crude powers of detecting selective advantages in nature by direct observation. Obviously a means of detecting in nature selective intensities of this order, and I suspect that the intensity of natural selection is seldom much greater, would be an enormous step towards putting the theory of selective adaptation upon a quantitative basis. It would, for example, be of the very highest interest if you found that the proportion of dominants, and therefore the selective advantage of the colour pattern, varied from place to place, for this would open up a whole new field in the quantitative study of ecological conditions. The subject may, indeed, well prove to be of astonishing intricacy, but it will be a great step to have opened the door to its exploration.

If everything were going to be as simple as the example I have written about above, I do not think difficulties would arise in the interpretation of smaller samples of 200 or 300, if it happened to be difficult to collect the larger number. The main difficulty I can foresee is that the multiple dominants may either be double heterozygotes in repulsion or in coupling, and, owing to high linkage, these latter should be regarded as dominant compounds almost as stable as the single dominants, and existing therefore with a frequency appropriate to the selective advantage of the compound phenotype (and the selective disadvantage of the doubly homozygous dominant) which may not be simply related at all to the selective advantages of the simple phenotypes of which they are compounded. It may be that dominant compounds in coupling are really rare in nature, in which case my anxiety on this head is groundless, but, if not, the situation may need a rather intricate discussion and it might prove very advantageous to preserve

multiple dominants alive, or at least a sample of the commoner compounds, with a view to testing their genetic constitution. But this, though it would greatly aid the interpretation of the sample, may prove to be impossible in practice.

I can only wish the best of luck to your hunting and hope perhaps I may meet you and Dr. Nabours at the Genetical Congress at the end of this month.

Fisher to R.K. Nabours: 22 February 1933

I have your interesting letter and enclosures. May I say at once that you put your proposals in such a way as to ensure that I shall co-operate with the greatest pleasure. I hope you will act, as it were as editor, receiving notes from me from time to time, and deciding what to do with them, i.e. inclusion in a joint paper, or leaving over for separate publication. I enclose three notes at once, on the remote chance of being in time for a small modification of your paper for *Genetics*. I fear, however, that even if you agree entirely with me, my notes will be too late.

Fisher to R.K. Nabours: 27 February 1933

I enclose another note, the last probably for some little time, this time on some associations in *Paratettix cucullatus* and some inferences from them. I understand that you have a body of breeding data, hitherto unpublished, which you intend to send me next June. In the meantime I should be glad to have offprints of all your previous publications on the grouse locusts, so far as you can spare them to me, with a bibliography of any that you cannot spare, or perhaps, better still, an inclusive bibliography, so that I shall not miss the point of any new information that becomes available. I should particularly value the offprints as with these I could use what time I have to the best advantage; and the data in them may suggest further inquiries which the original material in your possession may be capable of answering.

I should like, when I have done with them, to present the collection of identified phenotypes which you have sent me, to the Natural History Museum in this country, but before doing so I should be glad to be sure that this step would meet with your approval.

Fisher to R.K. Nabours: 22 March 1933

I was afraid my notes could not be got to you in time for the insertion of any reservations in the *Genetics* paper.[79] I can entirely sympathize with your desire to get an additional note printed in time for circulation with your reprints, for whenever I have seen reason to modify or abandon a scientific opinion, I have been extremely impatient to put myself right in public.

Nevertheless, looking at the thing dispassionately I do not see in this case much need for haste.

I had supposed that, in the event of you and Sabrosky finding my notes convincing on linkage in *Acrydium arenosum*, that we might take up that topic later in a joint paper, perhaps after further experiments had made the evidence more decisive. The fact that you are giving up experimenting with this species, however, is a point in favour of publishing at once, and how we should do this depends, I think, on how fully you and your colleague accept the probable validity of the alternative interpretation of the linkage data which I have based on your experimental observations.

Provided you find yourself in agreement with my general conclusions, that is that there is a single long, and probably linear, linkage group, the physical basis of which *may* be a single chromosome, but may again, possibly, be several chromosomes, more of less frequently associated in transmission (e.g. by occasional attachment) then I believe the best course would be for you to incorporate my arguments and calculations in a supplementary note under our joint names, to be published in *Genetics* if the editors will expedite the supply of offprints to you, or in the *American Naturalist* if they would supply the stuff quicker. This would have the advantage, which separate publication by me would lack, that it would not give the impression that, after considering the evidence, we took different views of its interpretation, when, in fact, as I am now postulating, we agree entirely as to the main inferences. I should, therefore, be perfectly content, if, merely to save time, you were to embody the chief points of my letter in a short note to either of these journals, if necessary without delaying even to let me see the proofs.

With respect to your application to the National Research Council, I shall, if consulted, do most heartily all that I can to forward it. For, confident as I was two years ago that the direct determination of the frequencies in Nature of the forms of polymorphic species which had been subjected to a sufficient genetical analysis would throw a direct light on problems connected with the evolution of dominance, now that I have seen your data for the collections of last year I am more fully convinced of the richness of the biological field opened up by such observations.

Assuming that the long linkage group in *Acrydium arenosum* is homologous with the very short linkage groups of most of the other species it should be possible to throw new light on a very important problem, to which I have found, so far, no satisfying solution. For on this view it is probable that in this species, unlike most of the others, crossing over has become progressively more and more frequent in all parts of the chromosome. Now a selective agency producing progressively closer linkage has attracted my attention for some years, and is very demonstrably present in the species for which you have counted a sample of the wild population. Such a selective

action is always at work when two factors in the same linkage group are both in equilibrium in such a way that each greatly affects the selective advantage of the other. Your data supply a great abundance of cases where the frequency of one dominant is largely influenced by the presence or absence of another so that this particular agency, acting constantly towards closer linkage, must be particularly active and widespread in the grouse locusts. Such a supposition accords perfectly with the fact that in most of your species the linkage of the factors governing polymorphism is found to be extremely close. Now I have never satisfied myself as to what agency in Nature usually counterbalances the action of the agency considered above, so as to maintain any recombination at all among linked factors. Some selection in favour of looser linkage must be exerted by progressive evolutionary changes, though I have never been able to see how this could be great enough quantitatively. This linkage loosening effect might, I suppose, be much enhanced in a species which had recently experienced great changes in environment either by spreading into new habitats or by its ecological situation, including its predators, being much affected by human occupation. And some such circumstance may afford a clue to the case of *Acrydium arenosum*.

Perhaps the ideal form of selection for loosening linkage in general would be one in which one set of pattern combinations was highly selected for a few generations and a totally different complementary set were just as highly selected a few generations later. Seasonal selection, e.g. fertility in summer versus viability in winter, might perhaps really work in some such way, but if I am right in supposing that *Acrydium arenosum* is exceptional, and isolated from the others of its group in respect to its linkage, I should be inclined at first to guess that the cause of its exceptional character should be sought rather in some transient and exceptional circumstance of its recent evolutionary history. A good guess here which turned out later to be verifiable might, I think, lead to quite a big step forward.

I am exceedingly glad to hear there is now a prospect of collections from Southern Mexico especially in view of the possibility of bringing them into comparison with the genetical data already in your possession on *Apotettix*. I believe, however, that you have also secured perhaps equally extensive genetical data of some other species which, having been published more summarily, have not yet given an opportunity of verifying the deficiency of homozygous dominants found in the *Apotettix* data. I think it would be very desirable, both for its own sake and for the sake of detailed comparison with the frequencies in Nature, if at least the matings giving information on this point could be sorted out.

Fisher to R.K. Nabours: 20 June 1933

I am exceedingly glad to hear that the plans for the collecting trip in Mexico

are now to be fulfilled. I wish you the very best of luck, and hope you will be able to make big collections at a variety of localities. These should be extremely instructive.

I hope before you go you will be able to send me the breeding data on *Acrydium arenosum,* and any other species, in which there are data bearing on the viability of the homozygotes. I much want to compare these with the frequencies in Nature.

Fisher to R.K. Nabours: 20 September 1933

I enclose:

(A) A discussion of the association of Mahogany (**My**) and white (**W**) in *Acrydium arenosum.* The full details of the calculation would be extremely tedious, and even what I have given is perhaps too much; the principle of using inequalities does seem, however, to be worth putting on record. I conclude that +/**My** individuals must have a low viability in Nature to the extent of about 42 per cent elimination, and that the association observed cannot be explained by differential fertility alone. The discussion is incomplete until you can tell me what your breeding experience has been with **W** and **My** in the linkage tests. The questions which need answering are:

(i) Are your experimental progenies consistent with the view that **My** is eliminated in comparison with + to the extent of as much as 42 per cent, and in comparison with **W My** to the extent of nearly 50 per cent?

(ii) If not, the balance must be made up by elimination in Nature due to causes not operative in the genetical material.

(iii) Is there any indication of reduced fertility of **My** individuals? A list of all broods or matings involving **My** would enable me to finish the discussion.

(B) A discussion of the same species, logically prior to (A). The chief point here upon which I should like supplementary information is as to whether the observed presence of any other dominants could mask the presence of **W**. If this is not possible, I think the conclusion of a selective aversion of **W** from most of the other dominants is well established, and it is interesting and important that this selection seems to act in alternate generations on the summer brood.

(C) A discussion, much of which I think you have seen, of *Paratettix cucullatus.* ...

I have a good deal more stuff, but am sending this so that we can get on with it bit by bit.

Fisher to R.K. Nabours: 7 September 1938

Very many thanks for your letter of July 11th. I am enclosing a short list of papers on grouse locusts which I do not possess and which I should be glad to add to my collection.

This year, at the British Association, I took the liberty of discussing the data you obtained with one species, *Paratettix texanus,* in your expedition of 1933, using your facts as a demonstration—which I think they validly are—of the existence of high selective intensities in wild conditions. I had been feeling, like you, that it was time the publication of discussion of these results was begun, and I thought, for my own part, that research would be furthered by the knowledge of how much you had succeeded in doing. If you think it fitting, I propose to publish, from time to time, papers on different aspects of the data which you sent me, with the obvious acknowledgements for this kindness, and with the quite unabashed hope that you will send me more when you come by it.[80]

Perhaps I told you that I tried to breed the two British species in this Laboratory, but was unsuccessful. Perhaps I shall try again later if I have the opportunity.

Fisher to A.J. Nicholson: 5 May 1955

Thank you for your letter. ... The difference in the matter of adaptation is indeed, I think, rather fundamental, for I feel sure that Darwin would never have made his discovery had he not been remarkably strongly impressed with the reality and intensity of adaptations. It was, I think, only the fading of this impression towards the end of the nineteenth century, which opened the door to theories of de Vries' 'mutation theory' type.

Fisher to J. Rasmusson: 8 August 1933

I was very glad to have your offprints and especially the Contribution to the Theory of the Inheritance of Quantitative Character.

With respect to yield, I am sure you are right that an interaction in the sense of a mutual inhibition of quantitative effects occurs in the neighbourhood in the maximum yield obtainable. I do not, however, like to apply this explanation to a character like plant height, which I am sure could be much increased in the case of cereals, at the expense of yield, if anyone cared to select solely for this character. But the delayed inbreeding effect, for which good published data seem almost lacking is certainly as recognizable in height as in yield and I wonder whether you have considered from this point of view the delay introduced in species, perhaps of recent tetraploid origin, in which many of the deleterious recessives occur as duplicate pairs or triplicate trios.

I am inclined to suggest, in fact, that good data on progressive inbreeding might in some characters afford a basis for estimating the proportion of recessives which belong to duplicate pairs, but this calculation would only be valid if interactions could be neglected entirely.

When you have time let me know what you think about this.

Fisher to J. Rasmusson: 1 January 1934

I have just received your very welcome letter of December 21st, but have scarcely considered all the good points in it. I am very glad that we do not really disagree as to the possible influence of duplicate factors, and its relation to interaction, which term I have been inclined to think of rather physiologically than genetically, if such a distinction may be permitted. I mean that the effect on the gene might be expressible to a good approximation in terms of some phenotypical quantity, such as the height of plant. At different heights then, the gene would have different effects, but at the same height much the same effect by whatever complex of other genes that height is determined. This would be what I think of a physiological kind of interaction, but it might be also that the effect of a gene is expressible to a good approximation in terms of the other genes present, or some few of them, and not simply related to their aggregate phenotypical expression, and this I would call a genetical interaction. Some day you and I must devise experimental procedures fit to disentangle these two possibilities.

I do not at all understand Haldane's remarks about 'Dominance Theory'.[81] I am in doubt, as I suppose all good men of science must be, in the sense that there is very little that I would wish to be dogmatic about, but I am more firmly convinced than I was when I wrote in 1928, and not less firmly so, as to (1) the modifiability of dominance, (2) that most mutations now recessive have become so progressively since their first appearance, (3) that the dominants in polymorphic species produce external effects which are beneficial and balanced in nature by a lower viability in the homozygote, (4) that most of the so-called dominants in poultry are really quite incompletely dominant. There is a great deal more that I should like to be sure of, especially in relation to the complex linkage systems in the polymorphic species.

I was interested in re-reading East and Jones's *Inbreeding and Outbreeding* to see what I had overlooked, that in 1919 they already felt the need of an evolutionary explanation for the great excess of recessives among mutations, and suggest that natural selection has eliminated those types which would be most inclined to dominant mutations. They do not, however, discuss numerically the selective intensity available to alter the mutation rates, and indeed such a selective action would really be trifling in magnitude for mutation rates not much higher than one in a million. It might, I think, be reasonably argued that the type of selection suggested by East and Jones provides the reason why mutation rates in general do not seem as high as one in a thousand, or one in ten. ...

Fisher to C. Tate Regan:[82] 7 February 1927

Many thanks for your letter. ...

Re Mendelism and Evolution, I will not inflict on you a full argument, but put more briefly a few points on which I should particularly like to have your opinion, and which can be enlarged upon if they interest you.

As you know, I regard the 'saltation' view as a pre-Mendelian preconceived idea which has led to a quite erroneous interpretation being put upon the bearing of Mendelian laws of inheritance upon evolution theory.

Where the Mendelian facts seem really to help is on the questions of variation, discussed in the first two chapters of the *Origin*; and here, I suggest, they require a somewhat fundamental rearrangement of ideas. About 1857 the idea crossed Darwin's mind (letter to Huxley, *More Letters,* Vol. [I] No. [57]) that inheritance might not be of a 'blending' but of a 'particulate' character. Possibly sexual dimorphism suggested the idea, but it was not followed up, and the reasoning of the Chapters referred to, and especially of the corresponding sections of the earlier essays, is based on blending. As I understand it the following argument is developed (I should immensely like to know if you think I have reproduced it rightly); by pure blending inheritance sexual reproduction will rapidly produce uniformity (in modern terms the variance will approximately be halved in every generation); consequently variation must be ascribed to the almost contemporary action of external conditions, the effect of this action being much influenced by the nature of the reacting organisms. Great variability is shown by domesticated animals and plants of very different kinds; consequently we may look for pecularities in the environment common to all domesticated species as probable causes of variability. The two peculiarities which seem to be common to all cases are 'changed conditions' and increased food, with crossing of varieties already formed, which is regarded as acting in a manner analogous to changed conditions, as a secondary cause.

One difficulty here did not escape Darwin; comparing those species which have been longest domesticated with those more recently domesticated, the former seem to be not less but more variable. But the great change of conditions took place long ago, and the food cannot have continued throughout the whole period to increase greatly. It is inferred that there must be some delayed or cumulative action upon the reproductive system which shall explain this fact.

In order to apply selection theory to wild species, it was necessary to show that they, like domesticated species, actually showed heritable individual differences; on this point Darwin had little direct evidence, especially when the first chapters were sketched out in the earlier essays. But, if the cause has been rightly assigned for the case of domesticated species, it can be argued that occasionally in nature the conditions change abruptly, and sometimes increased food will be available, and so to infer that analogous heritable individual differences will be produced. All this inference can be placed on a definite basis of observation by showing that the wild species do in fact show individual heritable differences.

What difference will it make to the above argument if we replace blending by particulate inheritance? First, whereas in blending inheritance heritable variability will only be maintained if almost every individual of every generation is a mutant (shows or possesses heritable novelties), in a particulate system there is no inherent tendency for the variability to die out. The genes will merely be recombined in each generation with a total variability almost unchanged. Two causes may be pointed out which do tend towards uniformity: (i) random survival, and (ii) selective survival. With random survival a gene will occasionally become exterminated by chance; the effect of this on the variance (which has been thought to be very great by the Hagedoorns) may be easily calculated, and I find that if n individuals reproduce in each generation, the variance will be halved in $2.8 \times n$ generations.[83] This will be an enormous time with most species, and the effect in any case is quite negligible compared to that of moderate rates of selection. Selection does really produce a tendency to uniformity, and this must be counterbalanced by occasional mutations. I have made some calculations to get an idea of the order of quantities involved. Take mean selection rates at 1%, representing that owners of a particular gene leave on an average 1% more or less offspring than owners of its allelomorph; take a population of only a million parents of each generation. Then if one in a million of the offspring is a tolerably good mutant, the number of factors maintained in the species will not fall below 100. By a tolerably good mutant I mean one which is not quite hopeless, but which in certain circumstances, or in certain genetic combinations, may be advantageous, but on the whole is neutral.

In interpreting this last calculation one may note [the following points].
(i) 100 factors form a somewhat ample reservoir of heritable variability. The number of pure breeding genotypes is 2^{100}, the number of heterozygous types bringing the total up to 3^{100} (48 figures in decimal notation). A population of a billion or so can only test a minute fraction of such combinations in each generation. By gradually varying the gene proportions, combinations which at first would be hopelessly improbable in a population of 10^{12}, would be made quite frequent, and vice versa so that continuous progressive evolution of the specific type would not have to wait upon the occurrence of fresh mutations. If mutation were altogether to cease, evolution would still go on carrying the species mean far beyond the original limits of individual variation, though of course in this case progress would ultimately cease when the supply of variance became exhausted.
(ii) Mutations themselves must be much more frequent that 1 in a million. The measured mutation rates for individual factors in *Drosophila* and Maize are of the order of 1 in 10^5, and there are evidently some thousands of different mutations possible. Probably about 20 million fruit flies have been examined from experimental cultures and at least 500 mutants (of the limited class which are useful to geneticists) have turned up. The lethals are

distinctly more numerous; in view of these facts it does not seem improbable that mutations of the equally limited class designated by tolerably good should appear once in a million new individuals.
(iii) The population number of 10^6 parents in each generation represents a somewhat small species. I suppose most species lie between 10^6 and 10^{12}, though some, such as some of the millipedes, certainly exceed the latter figure. The larger the population the less frequent need mutations be to maintain a given stock of segregating factors, or in other words, with the same mutation rates the larger will the variance (when equilibrium is attained) be.

I suggest that if Darwin had ever recast his argument in terms of particulate inheritance he would have perceived at once the solution of the delayed or cumulative effect of domestication upon variability, namely that existing variability is due to mutations which may have occurred at any time since the first domestication. The greater variability of domesticated species would then be due not necessarily to any change in mutation rates, but to the greater chance of the survival of oddities under domestication. The increased variability found after crossing distinct varieties finds an obvious explanation, which throws much doubt on the analogy between crossing and changed conditions. The emphasis laid by Darwin upon the view that the most important effect of changed conditions was to produce a general variability through indirect action on the reproductive system, while he could only find slight evidence of direct action with a uniform heritable response, accords with the modern view that environment seldom or only with difficulty acts in determining specific mutations, while it is all-powerful in determining whether mutations in general shall or shall not survive and contribute to the general variability.

The main feature which distinguishes the particulate from the blending theory of inheritance is the great rarity of mutations in the former, and their extreme frequency on the latter theory. The exclusive applicability of the former theory even to cases incapable of Mendelian analysis, such as the quantitative normally distributed characters which seem to blend, like human stature, is shown by a variety of facts, of which the only one I need mention is their behaviour in pure lines. Johannsen has reported two heritable mutations among many thousands of his beans, but apart from these, heritable variability appears to be totally absent, selection over ten or more generations producing no visible effect. Now in blending inheritance almost all the heritable variability is less than 10 generations old; so practically the full heritable variability of the blending type, if any existed, would be available. I conclude that the inheritance appears to be exclusively particulate.

Now for your vertebrae![84] In herring samples only 3 or 4 vertebrae numbers appear, but these are distributed numerically like grouped normal date; i.e. they suggest an underlying continuous variate of vertebra potenti-

ality which can only express itself in development to the nearest whole number. The *Zoarces* inheritance tables strongly confirm the same view, and Schmidt's diallel experiment with fowls seems to prove it conclusively with this group. In the latter the potential value deduced from averages of offspring may differ by more than half a unit from the actual, which is what would be expected if either developmental environment played a part as in human stature, or if Mendelian dominance produced a discrepancy between the parental genotype and its average expression in the offspring. In *Zoarces* the fact that the fraternal correlation is higher than the parental is direct evidence for Mendelian dominance.

In groups in which all or nearly all the individuals have the same vertebra number, two views are possible: (i) there is no genetic variability, (ii) neither genetic variability, nor the variability of the developmental environment, is sufficient to produce frequent departures from the central integer. The first view is improbable in view of the previous conclusions, because a mutant gene affecting vertebra number potential, unless it have other effects, will be exempt from selection, and consequently such mutations as have occurred in the past should accumulate, at least so long as the vertebra number is not actually changed.

If we take the second view, heritable individual variation exists in respect of the tendency to produce a given number of vertebrae, and the species is therefore potentially plastic in this respect. Supposing the mean of this distribution coincides with the modal integer (which of course is not the case in herring samples), one would have (i) if the S.D. of the distribution was 1/6 of a unit, only 3 exceptions in a thousand individuals taken at random, (ii) for 1/8 of a unit only 63 in a million, (iii) for 1/10 of a unit only 1 in two million, and so on. Very large counts would be needed to exclude these possibilities, which would, however, supply a *point d'appui* for selection.

Here I expect you to protest that in the case I have sketched there would be no reason for a large assemblage of related species to have the same number, but that more probably each would find it convenient to fix upon its own optimum number. The agreement of many different species is, in fact, an argument for genetic invariability. The case is singularly like that of the neck vertebrae in mammals. If I make a suggestion, it is one which I confidently expect you to be able to obliterate, but I hope you will consider whether it cannot be replaced by a better informed suggestion of similar effect.

My suggestion is that a certain extra-stability in respect of meristic changes might be expected in species, because it might reasonably be anticipated that the introduction of an extra vertebra should cause some degree of disorganization in the associated structures, attached muscles, nerves, blood vessels, etc., and even if there were a slight advantage to be gained by a complete reorganization on the basis of one more vertebra, it might well be that such slight advantage might be less than the disadvantage suffered

owing to such disorganization in any individuals which happened to have the higher number. I imagine that in species such as the herring with variable vertebra numbers the morphological repetition of associated parts is complete, as far at least as can be traced morphologically, though even here one cannot be sure that all quantitative physiological adjustments, such as blood supply and nervous reflexes, have been completely coordinated. The occasional occurrence of fused vertebrae is an example of a partial morphological failure. In species with more constant vertebra number such disorganization is perhaps more confidently to be expected, if any individual happens to develop an abnormal number of vertebrae, because the developmental mechanisms, which must effect such readjustments, can have less opportunity of being perfected by selection.

Of course, I imagine that the selective differences both *pro* and *con* are exceedingly minute; modification follows so rapidly upon any pronounced selective advantage that the latter can scarcely ever come into play.

If there is any truth in this view it would follow that conservatism should often be the rule in meristic matters, in spite of the existence of heritable variability in the innate tendencies; but that if ... any pronounced change in habit, especially one affecting the use or attachments of the musculature, should be in progress, the merely conservative tendencies would cease to act.

Can you tell me if such modifications of associated structures are in fact found in the neck of sloths, or in the flat fishes, or other examples among the fishes of a break away from the conservative tradition of the parent stock?

I have not been so brief as I had hoped, but, believe me, I have put a great deal, through attempted brevity, much less convincingly than it ought to be put. You will, I am sure, not condemn any part of the argument on slight verbal grounds, but I should be pleased to explain any point which I have left in too hopeless obscurity.

Fisher to C. Tate Regan: 24 March 1928

Perhaps you will remember writing to me some time ago about fish vertebrae, when I suggested the possibility that variation was kept within bounds by the extreme variates being more frequently abnormal in development.

I had not then any numerical data, but put forward the possibility solely on the group of facts which you put before me. Since then, by the kindness of E. Ford at Plymouth, I have some data for herrings which bring out the point very beautifully (*Journ. Marine Biol. Ass.*, XIV, 413).

Ford has 95 fish with abnormal skeletons and nearly 7000 normals for comparison. If each element in a double or triple formation is counted as 1 vertebra, the means of the two groups agree closely, but the variations do not agree.

The abnormals are relatively infrequent in the central classes 55 and 56, which comprise about 90% of the fish, while they show an excess of frequency in classes 53, 54 and 57, 58. This seems to demonstrate, in the herring, the effect I postulated. It is well shown by the percentage abnormal in each class:—

Class	53	54	55	56	57	58
Percentage	46	4.1	1.2	1.1	2.6	10

You will see from this that there is a tendency for the rarer genotypes to produce abnormalities; and this, I suggest, explains the great constancy of vertebra numbers in groups in which no variations have been observed, without postulating the absence of genetic variability.

Fisher to C. Tate Regan: 3 April 1928

I am a little puzzled by your last, as you have not, I think, referred to the correspondence of last year. Very briefly the point is this. In the absence of evidence to the contrary, the Darwinian assumes that every character is affected by hereditary variations. The constancy of number in a meristic series in any one species is no argument against this view, for the heritable variation may have effects small compared to one unit; but, an assemblage of such species would be a difficulty, unless there were some tendency always or usually in action eliminating meristic variations as such. It seemed not improbable that such a tendency should exist, but if so, one might expect to find that malformations were more frequent in conjunction with rare vertebra numbers than in conjunction with common ones. The fact that this is so in the herring confirms what seemed at first sight to be a hazardous conjecture. This view of meristic variability has the advantage that it admits of the accumulation of heritable variance and of consequent changes in vertebra numbers at periods in which the reorganization of structures associated with the skeleton is in progress.

Fisher to C. Tate Regan: 12 April 1928

I am afraid you have got my views inside out, as I suggested that the constancy in vertebra numbers was due to the heritable variation being less than one unit in extent, and have been chiefly concerned to show how it is possible for it to have been kept so low. I have had the evolutionary part of my long letter of last year retyped so that you may have a copy by you, if you care to reply to this. I should be exceedingly glad to know if the attachments of the musculature, or other associated structures, do in fact show signs of modification in the groups which have broken away from the 24 vertebrae tradition.

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